PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 249/12, 249/10, 249/08, 401/04, 405/04, A61K 31/41 — A1

(11) International Publication Number: WO 99/14204

(43) International Publication Date: 25 March 1999 (25.03.99)

(21) International Application Number: PCT/US98/18170

(22) International Filing Date: 14 September 1998 (14.09.98)

(30) Priority Data:
60/059,018 16 September 1997 (16.09.97) US

(71) Applicant *(for all designated States except US)*: G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680–5110 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: SIKORSKI, James, A. [US/US]; 2313 East Royal Court, Des Peres, MO 63131 (US).

(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680–5110 (US).

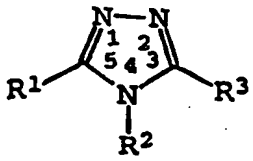
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUBSTITUTED 1,2,4–TRIAZOLES USEFUL FOR INHIBITING CHOLESTERYL ESTER TRANSFER PROTEIN ACTIVITY

(57) Abstract

A class of substitued 1,2,4–triazole compounds are described as useful for inhibiting the activity of cholesteryl ester transfer protein. Compounds of particular interest are defined by Formula (I), wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl; wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, hydroxy, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and wherein R^3 is selected from hydrido, –SH and halo; provided R^2 cannot be phenyl or 4–methylphenyl when R^1 is higher alkyl and when R^3 is –SH; or a pharmaceutically–acceptable salt or tautomer thereof.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Substituted 1,2,4-Triazoles Useful for Inhibiting Cholesteryl Ester Transfer Protein Activity

Field of the Invention

This invention is in the field of treating cardiovascular disease, and specifically relates to compounds, compositions and methods for treating atherosclerosis and other coronary artery disease. More particularly, the invention relates to substituted 1,2,4-triazole compounds that inhibit cholesteryl ester transfer protein (CETP), also known as plasma lipid transfer protein-I.

Background of the Invention

Numerous studies have demonstrated that a low plasma concentration of high density lipoprotein (HDL) cholesterol is a powerful risk factor for the development of atherosclerosis (Barter and Rye, *Atherosclerosis*, 121, 1-12 (1996)). HDL is one of the major classes of lipoproteins that function in the transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL) and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of

BNSDOCID: <WO___9914204A1_I_>

atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of atherosclerosis and other diseases associated with accumulation of lipid in the blood vessels. These diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

Atherosclerosis underlies most coronary artery disease (CAD), a major cause of morbidity and mortality in modern society. High LDL cholesterol (above 180 mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDH/LDL ratios. Inhibition of CETP by the subject compounds are shown to effectively modify plasma HDH/LDL ratios, and to check the progress and/or formation of these diseases.

CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, *J. Lipid Res.*, 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile

(McCarthy, *Medicinal Res. Revs.*, 13, 139-59 (1993); Sitori, *Pharmac. Ther.*, 67,443-47 (1995)). This exact phenomenon was first demonstrated by Swenson et al., (*J. Biol. Chem.*, 264, 14318 (1989)) with the use of a monoclonal antibody that specifically inhibited CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (*Biochim. Biophys. Acta* 795, 743-480 (1984)), Morton et al. (*J. Lipid Res.* 35, 836-847 (1994)) and Tollefson et al. (*Am. J. Physiol.*, 255, (Endocrinol. Metab. 18, E894-E902 (1988))) describe proteins from human plasma that inhibit CETP. U.S. Patent 5,519,001, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity.

There have been several reports of compounds that act as CETP inhibitors. Barrett et al. (*J. Am. Chem. Soc.*, 188, 7863-63 (1996)) and Kuo et al. (*J. Am. Chem. Soc.*, 117, 10629-34 (1995)) describe cyclopropane-containing CETP inhibitors. Pietzonka et al. (*Bioorg. Med. Chem. Lett*, 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al. (*Bioorg. Med. Chem. Lett.*, 5, 605-610 (1995)) describe Wiedendiol-A and -B, and related sesquiterpene compounds as CETP inhibitors. Lee et al. (*J. Antibiotics*, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids*, 25, 216-220, (1990)) describe

BNSDOCID: <WO___9914204A1_I_>

cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zilversmit (*J. Lipid Res.*, 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. describe 1,3,5-triazines as CETP inhibitors (Bioorg. Med. Chem. Lett., 6, 919-22 (1996)).

Triazole compounds are known. Kittur et al. (*J. Oil Technol. Assoc. India (Bombay)*, 18, 49-52 (1986)) describe 3-tridecyl-4-p-methylphenyl-5-mercapto-4-1,2,4-triazole compounds as antifungal and antibacterial agents. In U.S. Patents 3,701,784 and 3,769,411, Seidel et al. describe 1,2,4-4H-triazole compounds with fungicidal properties for controlling cereal rusts in plants. No pharmacologic properties are recited in either patent.

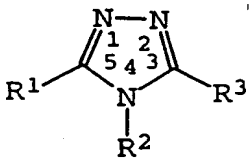
Bisgaier et al. (*Lipids*, 29, 811-8 (1994)) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor.

However, the 1,2,4-triazole derivatives of the present invention have not been described as inhibitors of CETP.

DESCRIPTION OF THE INVENTION

The present invention relates to a class of compounds comprising substituted 1,2,4-triazoles which are beneficial in the therapeutic and

prophylactic treatment of coronary artery disease as given in Formula I:



I

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, hydroxy, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl or 4-methylphenyl when R^1 is higher alkyl and when R^3 is -SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

The compounds of this invention can be used to inhibit cholesteryl ester transfer protein (CETP) activity, thereby decreasing the concentrations of low density lipoprotein (LDL) and raising the level of high density lipoprotein (HDL), resulting in a

therapeutically beneficial plasma lipid profile. The compounds also can be used to treat dyslipidemia (hypoalphalipoproteinemia), hyperlipoproteinaemia (chylomicronemia and hyperapobetalipoproteinemia), peripheral vascular disease, hypercholesterolaemia, atherosclerosis, coronary artery disease and other CETP-mediated disorders. The compounds can also be used in prophylactic treatment of subjects who are at risk of developing such disorders. The compounds can be used to lower the risk of atherosclerosis. The compounds of Formula I would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

A class of compounds of particular interest consists of those compounds of Formula I wherein R^1 is selected from C_{10-15} alkyl, C_{10-15} alkenyl, C_{10-15} alkynyl, aryl, aryl-C_{1-12}-alkyl, aryloxy-C_{1-4}-alkyl, arylthio-C_{1-4}-alkyl, higher alkoxyalkyl, higher alkylthioalkyl, and cycloalkyl-C_{1-12}-alkyl; wherein R^2 is selected from aryl, 5-6 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower alkoxy, halo, lower haloalkyl, lower alkylthio, lower alkylsulfinyl, lower

alkylsulfonyl, aryloxy, lower aralkoxy, aryl, lower aralkyl, aminosulfonyl, amino, lower monoalkylamino and lower dialkylamino; and wherein R^3 is selected from -SH, chloro and hydrido; or a pharmaceutically-acceptable salt or tautomer thereof.

A class of compounds of more particular interest consists of those compounds of Formula I wherein R^1 is selected from tridecyl, undecyl, dodecyl, tetradecyl, pentadecyl, (heptylthio)pentyl, methoxyundecyl, dodecynyl, tridecynyl, tetradecynyl, (heptylphenyl)methyl, (octylphenyl)methyl, (nonylphenyl)methyl, (decylphenyl)methyl, (hexylphenoxy)methyl, (octylphenoxy)methyl, (heptylphenyoxy)methyl, (hexylphenyl)propyl, (octylphenyl)propyl, (heptylphenyl)propyl, decylthiomethyl, undecylthiomethyl, ethylthiodecyl, and (undecyloxy)methyl; wherein R^2 is selected from cyclohexyl, naphthyl, pyridyl, and phenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower alkoxy, halo, lower haloalkyl, phenoxy, methylenedioxy, benzyloxy, lower alkylthio, and lower dialkylamino; and wherein R^3 is SH; or a pharmaceutically acceptable salt or tautomer thereof.

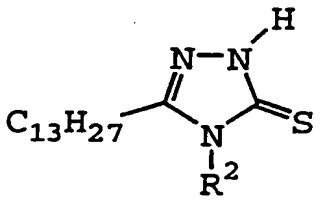
A class of compounds of even more particular interest consists of those compounds of Formula I wherein R^1 is selected from undecyl, dod cyl, tridecyl, tetradecyl, pentadecyl, tridecynyl, (heptylphenyl)methyl, (octylphenyl)methyl,

(nonylphenyl)methyl, (decylphenyl)methyl, (heptylphenyl)propyl and (octylphenyl)propyl; wherein R^2 is selected from cyclohexyl, naphthyl, and phenyl, wherein R^2 is substituted by one or more radicals independently selected from methyl, fluoro, chloro, methylthio, benzyloxy, phenoxy, methoxy, ethoxy, methylenedioxy, and trifluoromethyl; and wherein R^3 is SH; or a pharmaceutically acceptable salt or tautomer thereof.

Another class of compounds of more particular interest consists of those compounds of Formula I wherein R^1 is selected from (heptylthio)pentyl, tridecynyl, (undecyloxy)methyl, ethylthiodecyl, (heptylphenyl)methyl, (octylphenyl)methyl, (nonylphenyl)methyl, (decylphenyl)methyl, (heptylphenyl)propyl, (octylphenyl)propyl, and undecylthiomethyl; wherein R^2 is methoxyphenyl; and wherein R^3 is -SH; or a pharmaceutically acceptable salt or tautomer thereof.

Another class of compounds of more particular interest consists of those compounds of Formula I wherein R^1 is tridecyl; wherein R^2 is selected from naphthyl, methylphenyl, methoxyphenyl, and benzodioxolyl; and wherein R^3 is hydrido; or a pharmaceutically acceptable salt or tautomer thereof.

A subclass of compounds of Formula I of particular interest consists of compounds of the Formula II:



II

wherein R^2 is selected from lower cycloalkyl, naphthyl and phenyl substituted with one or more radicals independently selected from halo, lower alkoxy, lower haloalkyl, lower alkyl, lower alkylthio and lower aralkyloxy; provided that R^2 cannot be 4-methylphenyl; or a pharmaceutically acceptable salt or tautomer thereof.

A preferred class of compounds of Formula II comprises those compounds wherein R^2 is selected from naphthyl and phenyl substituted with one or more radicals independently selected from lower alkoxy, halo and lower haloalkyl.

A family of specific compounds of particular interest within Formula I consists of compounds, pharmaceutically-acceptable salts and derivatives thereof as follows:

2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-fluorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(3-chlorophenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-cyclohexyl-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-pyridyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-ethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2,6-dimethylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-phenoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(1,3-benzodioxol-5-yl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(2-chlorophenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(3-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-fluorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(3-chloro-4-methylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(4-benzyloxyphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(4-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(1-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4,-dihydro-4-(4-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3,4-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

BNSDOCID: <WO 9914204A1 >

2,4-dihydro-4-(2,5-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methoxy-5-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(4-aminosulfonylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-dodecyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-tetradecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-undecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-pentadecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-[5-(heptylthio)pentyl]-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(tridec-12-ynyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(tridec-6-ynyl]-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(undecyloxy)methyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(ethylthio)decyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(4-octylphenyl)methyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-heptylphenyl)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-nonylphenyl)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

5-(4-decylphenyl)methyl-2,4-dihydro-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-hexylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

BNSDOCID: <WO 9914204A1 | >

2,4-dihydro-5-(4-heptylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-octylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-hexylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-heptylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-octylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

4-(2-naphthyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;

4-(3-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;

4-(4-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;

4-(2-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate; and

4-(1,3-benzodioxol-5-yl)-3-tridecyl-4H-1,2,4-triazole, nitrate.

The use of generic terms in the description of the compounds are herein defined for clarity. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylthio", it embraces linear or branched radicals having one to about 10 carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and the like. The term "higher alkyl" denotes linear or branched radicals having eleven to about twenty carbon atoms. Examples of such radicals include undecyl, dodecyl, tridecyl, tetradecyl, and pentadecyl. The term "higher alkenyl" denotes linear or branched

radicals having from 11 to about 20 carbon atoms and having one or more double bonds. Examples of such radicals include undecenyl, dodecenyl, tridecenyl, tetradecenyl, and pentadecenyl. The term "higher alkynyl" denotes linear or branched radicals having from 11 to about 20 carbon atoms having one or more triple bonds. Examples of such radicals include undecynyl, dodecynyl, tridecynyl, tetradecynyl, and pentadecynyl. The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and

BNSDOCID: <WO__9914204A1_I_>

dichloropropyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Preferred alkoxyalkyl radicals are "higher alkoxyalkyl" radicals having alkoxy radicals of six to fifteen carbon atoms. Examples of such radicals include octyloxypropyl and undecyloxymethyl. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Said "aryl" group may have 1 to 3 substituents such as lower alkyl, alkoxy, halo, hydroxy, oxo, amino and lower alkylamino. The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered

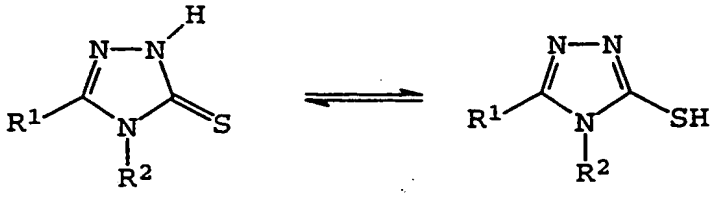
heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-

alkylthio" is methylthio (CH_3-S-). Also preferred alkylthio radicals are "higher alkylthio" radicals having seven to fifteen carbon atoms. An example of "higher alkylthio" is dodecylthio. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. Also preferred alkylsulfinyl radicals are "higher alkylsulfinyl" radicals having seven to fifteen carbon atoms. An example of "higher alkylsulfinyl" is dodecylsulfinyl. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical. The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The aryl in said aryloxy may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The aryl in said aralkoxy radicals may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl. The aryl in said aryloxyalkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio. The aryl in said arylthio may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl

and haloalkoxy. The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl. The aryl in said arylthioalkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. Also preferred alkylthioalkyl radicals are "higher alkylthioalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkylthioalkyl" is undecylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl. Also preferred alkoxyalkyl radicals are "higher alkoxyalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkoxyalkyl" is undecyloxymethyl.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

When R^3 is SH in Formula I, the compounds can be represented as either of the two tautomers shown below:



I^a I^b

Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

BNSDOCID: <WO 9914204A1 I_>

one to six carbon atoms. An example of "lower alkylthio" is methylthio (CH_3-S-). Also preferred alkylthio radicals are "higher alkylthio" radicals having seven to fifteen carbon atoms. An example of "higher alkylthio" is dodecylthio. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom. Also preferred alkylsulfinyl radicals are "higher alkylsulfinyl" radicals having seven to fifteen carbon atoms. An example of "higher alkylsulfinyl" is dodecylsulfinyl. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical. The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The aryl in said aryloxy may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The aryl in said aralkoxy radicals may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl. The aryl in said aryloxyalkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term

"arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio. The aryl in said arylthio may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl. The aryl in said arylthioalkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy. The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. Also preferred alkylthioalkyl radicals are "higher alkylthioalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkylthioalkyl" is undecylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl. Also preferred alkoxyalkyl radicals are "higher alkoxyalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkoxyalkyl" is undecyloxymethyl.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

When R^3 is SH in Formula I, the compounds can be represented as either of the two tautomers shown below:

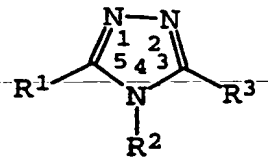
BNSDOCID: <WO__9914204A1_I_>

I^a I^b

Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a treatment and prophylaxis of coronary artery disease in a subject, comprising administering to the subject having such disorder a therapeutically-effective amount of a compound of Formula I'



I'

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a

substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, halo, alkoxy, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl when R^1 is tridecyl and when R^3 is SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

Compounds of Formula I' are capable of inhibiting activity of cholesteryl ester transfer protein (CETP), and thus could be used in the manufacture of a medicament or a method for the prophylactic or therapeutic treatment of diseases mediated by CETP, such as peripheral vascular disease, hyperlipidaemia, hypercholesterolemia, and other diseases attributable to either high LDL and low HDL or a combination of both. The compounds of Formula I' would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable

BNSDOCID: <WO___9914204A1_I_>

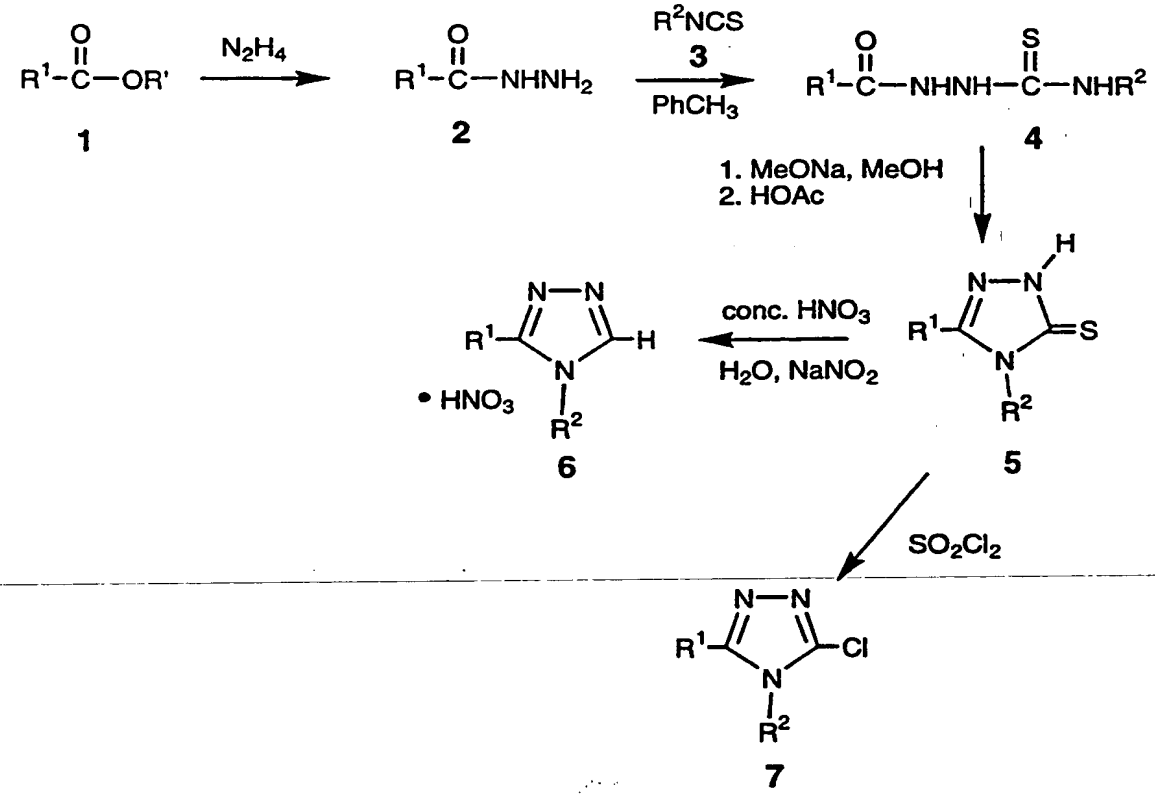
pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

BNSDOCID: <WO 9914204A1 I >

GENERAL SYNTHETIC PROCEDURES

The compounds of the present invention can be synthesized according to the following procedures of Schemes I-II, wherein the R^1 and R^2 substituents of the triazole ring are as defined for Formula I, above, except where further noted.

SCHEME I



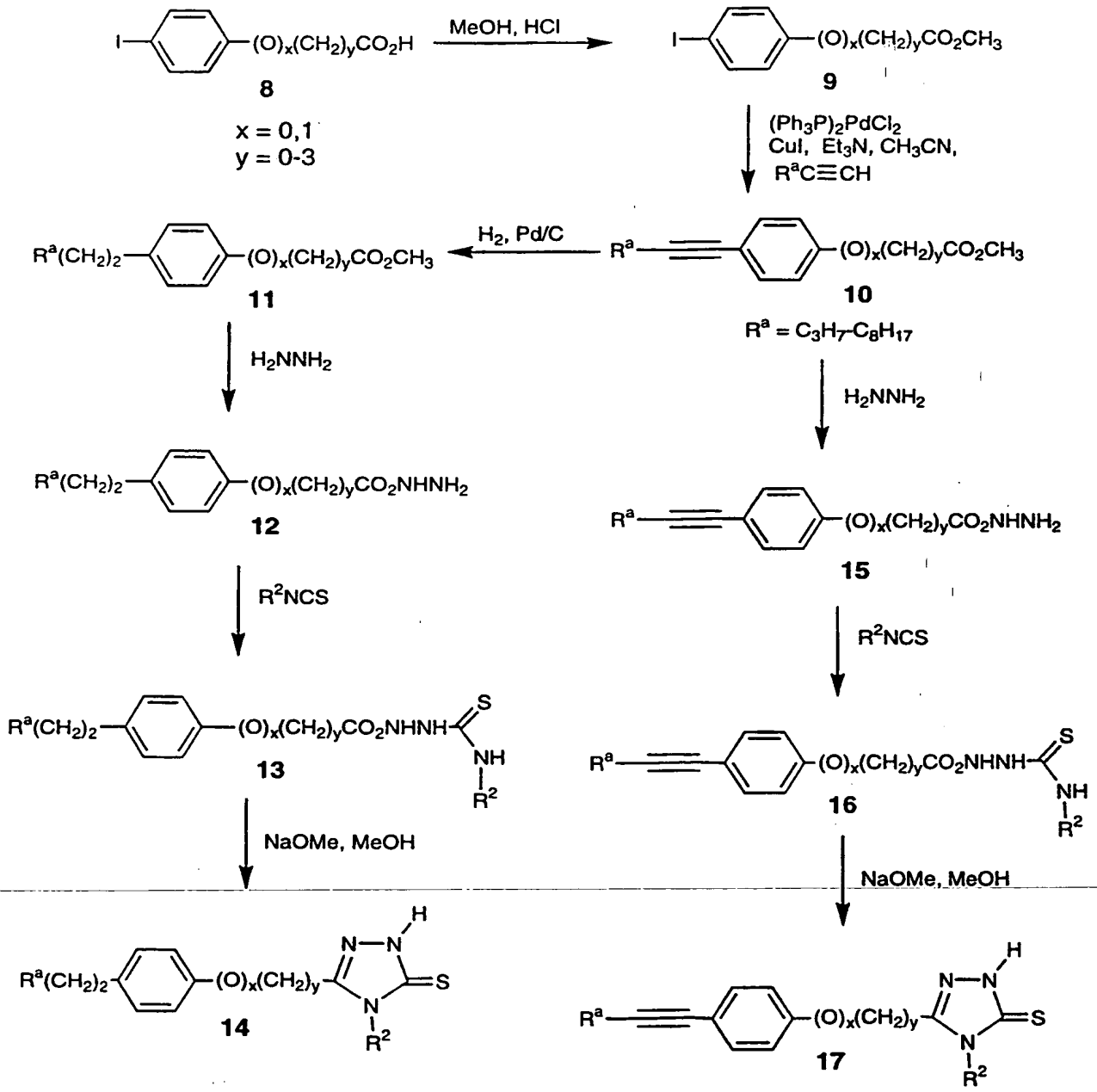
Synthetic Scheme I shows the preparation of 1,2,4-triazole-5-thione derivatives **5**. A suitable carboxylic acid ester **1** is converted to the corresponding carboxylic acid hydrazide **2** by

BNSDOCID: <WO 9914204A1 | >

heating with hydrazine in a suitable solvent such as methanol or ethanol. The resulting hydrazide **2** is then heated with an appropriate organic isothiocyanate **3** in a suitable aprotic solvent such as toluene. The resulting urea product **4** usually crystallizes from this solution upon cooling. Subsequent treatment of the isolated urea **4** with methanolic sodium methoxide produces the desired 1,2,4-triazole-5-thione **5**, which usually forms as a solid precipitate after acidification with acetic acid. Further reaction of the 1,2,4-triazole, such as with warm aqueous nitric acid and a catalytic amount of sodium nitrite produces the 1,2,4-triazole **6** as a solid nitrate salt. Alternatively, treating 1,2,4-triazole with neat sulfuryl chloride produces the 3-chloro-1,2,4-triazole **7**, after purification, such as by chromatography.

BNSDOCID: <WO 9914204A1 >

SCHEME II



Synthetic Scheme II shows the preparation of 1,2,4-triazole-5-thione derivatives **14** and **17** embraced by Formula I wherein a phenyl or phenoxy group containing a saturated or

BNSDOCID: <WO___9914204A1_I_>

unsaturated alkyl substituent has been inserted into the R^1 sidechain. In step 1, an appropriate p-iodophenyl- or p-iodophenoxy-alkyl carboxylic acid **8** is converted to its corresponding alkyl carboxylate ester **9** by heating in acidic alcohol. The resulting ester **9** is then coupled with an appropriate acetylene in the presence of a base, such as triethylamine and a suitable catalyst, such as bis-(triphenylphosphine)-palladium dichloride and cuprous iodide under an inert atmosphere and anhydrous conditions in an appropriate aprotic solvent, such as acetonitrile. The resulting coupled p-acetylene ester **10** may then be reduced by hydrogenolysis in the presence of a suitable catalyst, such as 10% palladium on carbon in a suitable solvent, such as methanol or ethyl acetate to give the corresponding saturated p-alkylphenyl or p-alkylphenoxy ester **11**. Ester **11** may then be converted to the corresponding hydrazide **12**, which can be treated with an appropriate organic isothiocyante, as described for Scheme I above, to give the urea **13**. Subsequent cyclization of urea **13** is achieved, such as with methanolic sodium methoxide which then gives the desired 3-(p-alkylphenyl)alkyl- or 3-(p-alkylphenoxy)alkyl-1,2,4-triazole-5-thione **14**, after acidification with acetic acid and subsequent purification, such as by chromatography.

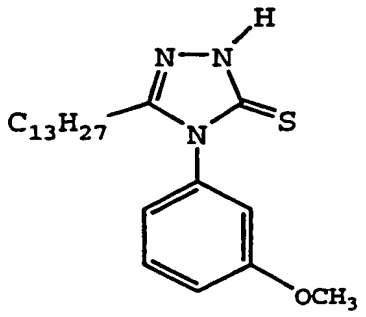
Alternatively, ester **10** may be reacted directly with hydrazine to give the

corresponding hydrazide **15**, which can be treated with an appropriate organic isothiocyante, as described for Scheme I above, to give the urea product **16**. Subsequent cyclization of **16** is achieved with methanolic sodium methoxide which then gives the desired 3-(p-alkynylphenyl)alkyl- or 3-(p-alkynylphenoxy)alkyl-1,2,4-triazole-5-thione **17**, after acidification with acetic acid and subsequent purification by chromatography.

One skilled in the art may use these generic methods to prepare the following specific examples, which have been properly characterized by ^{1}H NMR and mass spectrometry. These compounds also may be formed in vivo.

The following examples contain detailed descriptions of the methods of preparation of compound of Formula I. These detailed descriptions fall within the scope and are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are Degrees centigrade unless otherwise indicated.

EXAMPLE 1



2,4-Dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione

Step 1. Preparation of tetradecanoic acid hydrazide

As described in *J. Oil Technol. Assoc. India*, 11, 78-79 (1979), ethyl myristate (102.6 g, 0.4 mol) was combined with 25 mL of hydrazine monohydrate in 100 mL of ethanol. The resulting clear, homogeneous solution was stirred at room temperature for 30 minutes, then heated at reflux overnight. Upon cooling the clear homogeneous solution to room temperature, a voluminous white precipitate was produced which was collected by vacuum filtration, washed with cold ethanol and air-dried to give a white solid (72 g): m.p. 101-106 °C. Recrystallization from about 500 mL of hot ethyl acetate gave 56 g (58%) of the desired tetradecanoic acid hydrazide as white needles: m.p. 106.5-108 °C (lit. m.p. 114-115 °C). ^{1}H NMR (d_6-DMSO) δ 0.83 (t, J = 6.5 Hz, 3H), 1.22 (br s, 20H), 1.44 (m, 2H), 1.96 (t, J = 7.5 Hz, 2H), 4.11 (br s, 2H), 8.87 (br s, 1H). FABMS m/z = 243.4(M+H).

Step 2. Preparation of tetradecanoic acid 2-[[(3-methoxyphenyl)amino]thioxomethyl] hydrazide

Tetradecanoic acid hydrazide (Step 1)(1.6 g, 6.6 mmol) was combined with toluene (20 mL) and 3-methoxyphenyl isothiocyanate (1.2 g, 7.3 mmol). This mixture was heated to 60 °C and stirred for five hours. The heating was

stopped, and the solution was cooled to room temperature. A white precipitate formed which was collected by vacuum filtration. The resulting solid was washed with cold diethyl ether and air-dried to give 2.4 g (89%) of the desired tetradecanoic acid, 2-[[(3-methoxyphenyl)amino]thioxomethyl]hydrazide as a white solid: m.p. 109.4-111.4 °C. ^{1}H NMR CD_3CN δ 8.54 (s, 1H), 8.17 (s, 1H), 7.87 (s, 1H), 7.26 (t, J = 8.2 Hz, 1H), 7.16 (m, 1H), 7.02 (m, 1H), 6.78 (m, 1H), 3.78 (s, 3H), 2.24 (t, J = 7.5 Hz, 2H), 1.60 (m, 2H), 1.27 (m, 20H), 0.89 (t, J = 6.6 Hz, 3H). FABMS m/z = 408 (M+H). Calc'd for $C_{22}H_{37}N_3O_2S$: C, 64.83; H, 9.15; N, 10.31; S, 7.87. Found: C, 64.72; H, 9.20; N,10.37; S, 7.79.

Step 3. Preparation of 2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione.

Tetradecanoic acid, 2-[[(3-methoxyphenyl)amino] thioxomethyl] hydrazide (Step 2) (2.15 g, 5.28 mmol) was combined with methanol (10 mL) and a methanolic solution of sodium methoxide (1.6 mL of 25% sodium methoxide in methanol, 6.9 mL). This solution was stirred at room temperature while the progress of the reaction was monitored by HPLC. After three days at room temperature, the reaction was complete. The solution was filtered and acidified (pH 5) with acetic acid. Upon standing, a white solid formed, which was collected by vacuum filtration, washed with cold

BNSDOCID: <WO__9914204A1_I_>

methanol and cold diethyl ether, and air-dried to give 5-tridecyl-2,4-dihydro-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione as a white solid (1.34g, 65%): m.p. 91.5-93.7 °C. ^{1}H NMR (d_6-DMSO) δ 13.63 (s, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.08 (m, 1H), 6.99 (m, 1H), 6.93 (m, 1H), 3.77 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.40 (m, 2H), 1.20 (m, 20H), 0.83 (t, J = 6.2 Hz, 3H). FABMS m/z = 390 (M+H). Calc'd for $C_{22}H_{35}N_3OS$: C, 67.82; H, 9.05; N, 10.79; S, 8.23. Found: C, 67.71; H, 9.10; N, 10.80; S, 8.31.

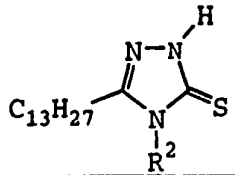
Additional examples of 2,4-dihydro-4-substituted-5-tridecyl-3H-1,2,4-triazole-3-thiones are prepared by one skilled in the art using similar methods from tetradecanoic acid hydrazide. These examples are summarized in Table 1.

Additional examples of 5-substituted-2,4-dihydro-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thiones can be prepared by one skilled in the art using similar methods from the appropriate fatty acids, fatty acid esters, or fatty acid hydrazides known in the literature, e.g., J. *Oil Technol. Assoc. India*, 11, 78-79 (1979); J. *Biol. Chem., 266,* 8835-8855 (1991). These examples are summarized in Tables 2 and 3, where Z represents an acetylenic linkage, and Y represents either a cis or trans -CH=CH- linkage.

3NSDOCID: <WO___9914204A1_I_>

SUBSTITUTE SHEET (RULE 26)

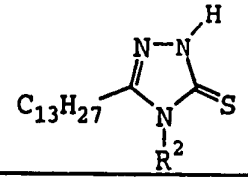
TABLE 1



Example No.	R^2	m.p.	Analyses
2	2-F-C_6H_4-	119.8-121.7	FABMS: m/z = 378 (M+H) HRMS: Calcd 378.2379 Found: 378.2391
3	cyclohexyl-	84-86	Calcd. C,68.99; H,10.75; N,11.49; S,8.77 Obs. C,68.97; H,10.79; N,11.45; S,8.71
4	2-CH_3-C_6H_4-	105.4-106.7	Calcd. C,70.71; H,9.46; N,11.25 Obs. C,70.67; H,9.45; N,11.30
5	3-Cl-C_6H_4-	--	FABMS: m/z = 394 (M+H)
6	2-CH_3O-C_6H_4-	139.6-140.8	Calcd. C,67.81; H,9.07; N,10.79 Obs. C,67.74; H,8.91; N,10.59
7	3-CH_3-C_6H_4-	139.0-140.8	Calcd. C,70.71; H,9.46; N,11.25 Obs. C,70.74; H,9.62; N,10.95
8	4-F-C_6H_4-	88.7-90.6	Calcd. C,66.79; H,8.59; N,11.13 Obs. C,66.44; H,8.51; N,11.21
9	4-C_6H_5O-C_6H_4-	106.4-107.5	Calcd. C,71.80; H,8.26; N,9.32 Obs. C,71.62; H,8.09; N,9.24
10	3-F-C_6H_4-	105.3-108.9	Calcd. C,66.79; H,8.59; N,11.13 Obs. C,66.75; H,8.53; N,10.87
11	3,4-(OCH_2O)-C_6H_3-	95.1-96.9	Calcd. C,65.47; H,8.24; N,10.41 Obs. C,65.42; H,8.11; N,10.40
12	4-CH_3-C_6H_4-	107.5-108.5	Calcd. C,70.71; H,9.46; N,11.25 Obs. C,70.60; H,9.32; N,11.26
13	2-Cl-C_6H_4-	153.7-154.9	FABMS: m/z = 394 (M+H) HRMS: Calcd 394.2084 Found: 394.2084

SUBSTITUTE SHEET (RULE 26)

TABLE 1 (continued)

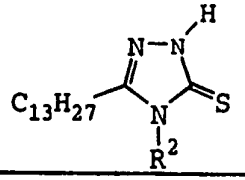


Example No.	R^2	m.p.	Analyses
14	4-CH_3O-C_6H_4-	84.1-86.3	Calcd. C,67.81; H,9.07; N,10.79
			Obs. C,68.15; H,9.12; N,10.91
15	3-CF_3-C_6H_4-	92.5-93.7	Calcd. C,61.79; H,7.56; N,9.83
			Obs. C,61.97; H,7.61; N,9.83
16	4-Cl-2-CH_3-C_6H_3-	86-87	FABMS: m/z = 408 (M+H)
			HRMS: Calcd 408.2240 Found: 408.2215
17	2-CH_3S-C_6H_4-	122.0-123.0	Calcd. C,65.14; H,8.70; N,10.36; S,15.81
			Obs. C,64.87; H,8.77; N,10.25; S,16.01
18	C_6H_5	95.5-96.5	FABMS: m/z = 360 (M+H)
19	4-$C_6H_5CH_2O$-C_6H_4-	123.7-124.8	Calcd. C,72.20; H,8.46; N,9.02
			Obs. C,72.14; H,8.40; N,8.90
20	2-naphthyl-	118.5-120.7	Calcd. C,73.29; H,8.63; N,10.26
			Obs. C,73.29; H,8.61; N,10.34
21	4-Cl-C_6H_4-	61.7-64.3	Calcd. C,64.00; H,8.20; N,10.66
			Obs. C,64.08; H,8.00; N,10.49
22	4-CH_3-3-Cl-C_6H_3-	99-102	FABMS: m/z = 408 (M+H)
			HRMS: Calcd 408.2240 Found: 408.2214
23	4-CF_3-C_6H_4-	59.7-63.8	Calcd. C,61.79; H,7.56; N,9.82
			Obs. C,61.82; H,7.45; N,9.80
24	3-$C_6H_5CH_2OC_6H_4$-	107.6-109.9	FABMS: m/z = 466 (M+H)
			HRMS: Calcd 466.2892 Found: 466.2897
25	3,5-$(CH_3O)_2$-C_6H_3-	120.2-122.4	Calcd. C,65.83; H,8.89; N,10.01; S,7.64
			Obs. C,65.71; H,8.94; N,10.00; S,7.60

BNSDOCID: <WO___9914204A1_I_>

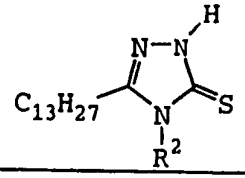
SUBSTITUTE SHEET (RULE 26)

TABLE 1 (continued)



Example No.	R^2	m.p.	Analyses
26	3-pyridyl-	135.4-137.0	Calcd. C,66.62; H,8.95; N,15.54; S,8.89
			Obs. C,66.64; H,8.86; N,15.56; S,8.80
27	$2\text{-}CH_3CH_2O\text{-}C_6H_4\text{-}$	116.8-118.4	Calcd. C,68.44; H,9.24; N,10.41; S,7.94
			Obs. C,68.60; H,9.32; N,10.38; S,7.91
28	$2,6\text{-}(CH_3)_2\text{-}C_6H_3\text{-}$	106.5-109.0	Calcd. C,71.27; H,9.62; N,10.84; S,8.27
			Obs. C,71.15; H,9.91; N,10.67; S,7.96
29	1-naphthyl-	161.0-162.5	Calcd. C,73.29; H,8.63; N,10.26
			Obs. C,73.41; H,8.57; N,10.10
30	$3,4\text{-}(CH_3)_2\text{-}C_6H_3\text{-}$	126.1-128.1	Calcd. C,71.27; H,9.62; N,10.84; S,8.27
			Obs. C,71.11; H,9.67; N,10.91; S,8.19
31	$4\text{-}CH_3S\text{-}C_6H_4\text{-}$	68.8-69.9	Calcd. C,65.14; H,8.70; N,10.36; S,15.81
			Obs. C,65.19; H,8.61; N,10.38; S,15.90
32	$3\text{-}CH_3S\text{-}C_6H_4\text{-}$	80.8-83.4	Calcd. C,65.14; H,8.70; N,10.36; S,15.81
			Obs. C,65.09; H,8.69; N,10.39; S,15.74
33	$2,5\text{-}(CH_3O)_2\text{-}C_6H_3\text{-}$	131.6-133.4	Calcd. C,65.83; H,8.89; N,10.01; S,7.64
			Obs. C,65.88; H,8.87; N,10.11; S,7.58
34	$2\text{-}CH_3O\text{-}5\text{-}Cl\text{-}C_6H_3\text{-}$	161.1-162.4	Calcd. C,62.32; H,8.08; N,9.91; S,7.56
			Obs. C,62.20; H,8.11; N,9.98; S,7.47
35	$4\text{-}(H_2NSO_2)\text{-}C_6H_4\text{-}$	188.4-191.4	Calcd. C,57.50; H,7.81; N,12.77; S,14.62
			Obs. C,57.30; H,7.76; N,12.75; S,14.46
36	$4\text{-}(CH_3)_2N\text{-}C_6H_4\text{-}$	145.2-146.3	Calcd. C,68.61; H,9.51; N,13.91; S,7.96
			Obs. C,68.52; H,9.53; N,13.84; S,7.89
37	$2\text{-}CH_3O\text{-}5\text{-}NO_2\text{-}C_6H_3\text{-}$	148.5-149.9	Calcd. C,60.80; H,7.89; N,12.89; S,7.38
			Obs. C,60.90; H,7.83; N,12.92; S,7.29

TABLE 1 (continued)



Example No.	R^2	m.p.	Analyses
38	3-NO_2-C_6H_4-	115.5-117.4	Calcd. C,62.35; H,7.97; N,13.85; S,7.92
			Obs. C,62.49; H,8.02; N,13.92; S,7.84
39	4-CH_3CH_2O-C_6H_4-	106.0-107.1	Calcd. C,68.44; H,9.24; N,10.41; S,7.94
			Obs. C,68.17; H,9.32; N,10.37; S,7.81
40	3,5-$(CH_3)_2$-C_6H_3-	145.7-147.1	Calcd. C,71.27; H,9.62; N,10.84; S,8.27
			Obs. C,71.18; H,9.64; N,10.79; S,8.22
41	2,5-$(CH_3)_2$-C_6H_3-	107.6-108.9	Calcd. C,71.27; H,9.62; N,10.84; S,8.27
			Obs. C,71.22; H,9.62; N,10.84; S,8.19
42	2-CH_3O-5-CH_3-C_6H_3-	126.5-127.5	Calcd. C,68.44; H,9.24; N,10.41; S,7.94
			Obs. C,68.24; H,9.18; N,10.37; S,7.86
43	2-CH_3-4-CH_3O-C_6H_3-	89.1-91.5	Calcd. C,68.44; H,9.24; N,10.41; S,7.94
			Obs. C,68.27; H,9.27; N,10.51; S,7.85
44	2,4-$(CH_3O)_2$-C_6H_3-	74.0-75.1	Calcd. C,65.83; H,8.89; N,10.01; S,7.64
			Obs. C,65.94; H,8.90; N,10.04; S,7.56
45	2,4-$(CH_3)_2$-C_6H_3-	90.4-93.0	Calcd. C,71.27; H,9.62; N,10.84; S,8.27
			Obs. C,71.13; H,9.99; N,10.94; S,7.97
46	3,4-$(CH_3O)_2$-C_6H_3-	111.4-114.3	Calcd. C,65.83; H,8.89; N,10.01; S,7.64
			Obs. C,65.82; H,8.95; N,10.03; S,7.58
47	3,4,5-$(CH_3O)_3$-C_6H_2-	108.8-110.7	Calcd. C,64.11; H,8.74; N,9.34; S,7.13
			Obs. C,64.31; H,8.73; N,9.36; S,7.03
48	2-CH_3O-4-NO_2-C_6H_3-	114.3-116.9	Calcd. C,60.80; H,7.89; N,12.89; S,7.38
			Obs. C,60.80; H,7.91; N,12.90; S,7.32

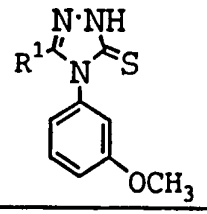
SUBSTITUTE SHEET (RULE 26)

SNSDOCID: <WO 9914204A1 >

BNSDOCID: <WO___9914204A1_I_>

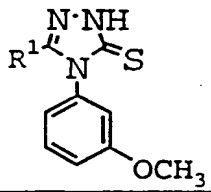
SUBSTITUTE SHEET (RULE 26)

TABLE 2



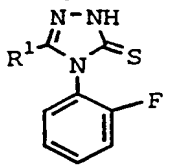
Example No.	R^1	m.p.	Analyses				
49	n-$C_{15}H_{31}$-	94.0-96.0	Calcd.	C,69.02;	H,9.41;	N,10.06;	S,7.68
			Obs.	C,68.91;	H,9.46;	N,10.14;	S,7.57
50	n-$C_{14}H_{29}$-	102.7-105.9	Calcd.	C,68.44;	H,9.24;	N,10.41;	S,7.94
			Obs.	C,68.49;	H,9.19;	N,10.47;	S,8.08
51	n-$C_{12}H_{25}$-	100.0-101.9	Calcd.	C,67.16;	H,8.86;	N,11.19;	S,8.54
			Obs.	C,66.60;	H,8.88;	N,11.14;	S,8.44
52	n-$C_{11}H_{23}$-	90.1-93.2	Calcd.	C,66.44;	H,8.64;	N,11.62;	S,8.87
			Obs.	C,66.39;	H,8.72;	N,11.65;	S,8.78
53	$CH_3CH_2S(CH_2)_{10}$-	89.4-90.5	Calcd.	C,61.88;	H,8.16;	N,10.31;	S,15.73
			Obs.	C,61.85;	H,8.22;	N,10.38;	S,15.81
54	$CH_3(CH_2)_{10}SCH_2$-	75.5-78.2	Calcd.	C,61.88;	H,8.16;	N,10.31;	S,15.73
			Obs.	C,61.95;	H,8.24;	N,10.36;	S,15.83
55	$CH_3CH_2O(CH_2)_{10}$-	91.2-92.3	Calcd.	C,64.42;	H,8.49;	N,10.73;	S,8.19
			Obs.	C,64.36;	H,8.53;	N,10.76;	S,8.12
56	$CH_3O(CH_2)_{11}$-	82.7-83.7	Calcd.	C,64.42;	H,8.49;	N,10.73;	S,8.19
			Obs.	C,64.32;	H,8.51;	N,10.81;	S,8.10
57	$CH_3(CH_2)_{10}OCH_2$-	oil	Calcd.	C,64.42;	H,8.49;	N,10.73;	S,8.19
			Obs.	C,64.32;	H,8.59;	N,10.72;	S,8.09
58	$CH_3(CH_2)_6S(CH_2)_5$-	waxy solid	Calcd.	C,61.88;	H,8.16;	N,10.31;	S,15.73
			Obs.	C,62.11;	H,8.13;	N,10.33;	S,15.70
59	$CH_3(CH_2)_5Z(CH_2)_5$-	waxy solid	Calcd.	C,68.53;	H,8.10;	N,10.90;	S,8.31
			Obs.	C,68.51;	H,8.16;	N,10.83;	S,8.23
60	$HZ(CH_2)_{11}$-	55.0-58.5	Calcd.	C,68.53;	H,8.10;	N,10.90;	S,8.31
			Obs.	C,68.55;	H,8.13;	N,10.94;	S,8.43

TABLE 3



Example No.	R^1	Example No.	R^1
61	$CH_3(CH_2)_6O(CH_2)_5-$	80	$CH_3(CH_2)_5O(CH_2)_6-$
62	$CH_3(CH_2)_6Z(CH_2)_4-$	81	$CH_3(CH_2)_5S(CH_2)_6-$
63	$CH_3(CH_2)_4Z(CH_2)_6-$	82	$CH_3(CH_2)_4O(CH_2)_7-$
64	$CH_3(CH_2)_3Z(CH_2)_7-$	83	$CH_3(CH_2)_4S(CH_2)_7-$
65	$CH_3(CH_2)_2Z(CH_2)_8-$	84	$CH_3(CH_2)_3O(CH_2)_8-$
66	$CH_3CH_2Z(CH_2)_9-$	85	$CH_3(CH_2)_3S(CH_2)_8-$
67	$CH_3Z(CH_2)_{10}-$	86	$CH_3(CH_2)_8O(CH_2)_3-$
68	$CH_3(CH_2)_5Y(CH_2)_5-$	87	$CH_3(CH_2)_8S(CH_2)_3-$
69	$CH_2=CH(CH_2)_{11}-$	88	$4-CH_3-C_6H_4(CH_2)_9-$
70	$CH_3(CH_2)_6Y(CH_2)_4-$	89	$4-C_2H_5-C_6H_4(CH_2)_7-$
71	$CH_3(CH_2)_4Y(CH_2)_6-$	90	$4-C_2H_5-C_6H_4(CH_2)_8-$
72	$CH_3(CH_2)_3Y(CH_2)_7-$	91	$C_6H_5(CH_2)_8-$
73	$CH_3(CH_2)_2Y(CH_2)_8-$	92	$C_6H_5(CH_2)_9-$
74	$CH_3CH_2Y(CH_2)_9-$	93	$C_6H_5(CH_2)_{10}-$
75	$CH_3Y(CH_2)_{10}-$	94	$C_6H_5(CH_2)_{11}-$
76	$C_6H_5S(CH_2)_9-$	95	$cyclohexyl(CH_2)_8-$
77	$C_6H_5O(CH_2)_9-$	96	$cyclohexyl(CH_2)_9-$
78	$CH_3(CH_2)_7O(CH_2)_4-$	97	$cyclohexyl(CH_2)_{10}-$
79	$CH_3(CH_2)_7S(CH_2)_4-$		

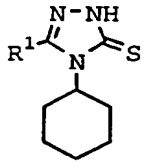
TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
99	$CH_3(CH_2)_5Z(CH_2)_5-$	119	$CH_3(CH_2)_6S(CH_2)_5-$
100	$CH_3(CH_2)_4Z(CH_2)_6-$	120	$CH_3(CH_2)_5O(CH_2)_6-$
101	$CH_3(CH_2)_3Z(CH_2)_7-$	121	$CH_3(CH_2)_5S(CH_2)_6-$
102	$CH_3(CH_2)_2Z(CH_2)_8-$	122	$CH_3(CH_2)_4O(CH_2)_7-$
103	$CH_3CH_2Z(CH_2)_9-$	123	$CH_3(CH_2)_4S(CH_2)_7-$
104	$CH_3Z(CH_2)_{10}-$	124	$CH_3(CH_2)_8O(CH_2)_3-$
105	$HZ(CH_2)_{11}-$	125	$CH_3(CH_2)_8S(CH_2)_3-$
106	$CH_3(CH_2)_5Y(CH_2)_5-$	126	$4-CH_3-C_6H_4(CH_2)_9-$
107	$CH_2=CH(CH_2)_{11}-$	127	$4-C_2H_5-C_6H_4(CH_2)_7-$
108	$CH_3(CH_2)_6Y(CH_2)_4-$	128	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
109	$CH_3(CH_2)_4Y(CH_2)_6-$	129	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
110	$CH_3(CH_2)_3Y(CH_2)_7-$	130	$4-C_2H_5-C_6H_4(CH_2)_8-$
111	$CH_3(CH_2)_2Y(CH_2)_8-$	131	$cyclo-C_6H_{11}(CH_2)_8-$
112	$CH_3CH_2Y(CH_2)_9-$	132	$cyclo-C_6H_{11}(CH_2)_9-$
113	$CH_3Y(CH_2)_{10}-$	133	$cyclo-C_6H_{11}(CH_2)_{10}-$
114	$C_6H_5O(CH_2)_9-$	134	$C_6H_5(CH_2)_8-$
115	$C_6H_5S(CH_2)_9-$	135	$C_6H_5(CH_2)_9-$
116	$CH_3(CH_2)_7O(CH_2)_4-$	136	$C_6H_5(CH_2)_{10}-$
117	$CH_3(CH_2)_7S(CH_2)_4-$	137	$C_6H_5(CH_2)_{11}-$

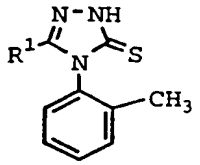
BNSDOCID: <WO___9914204A1_I_>

TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
139	$CH_3(CH_2)_5Z(CH_2)_5-$	159	$CH_3(CH_2)_6S(CH_2)_5-$
140	$CH_3(CH_2)_4Z(CH_2)_6-$	160	$CH_3(CH_2)_5O(CH_2)_6-$
141	$CH_3(CH_2)_3Z(CH_2)_7-$	161	$CH_3(CH_2)_5S(CH_2)_6-$
142	$CH_3(CH_2)_2Z(CH_2)_8-$	162	$CH_3(CH_2)_4O(CH_2)_7-$
143	$CH_3CH_2Z(CH_2)_9-$	163	$CH_3(CH_2)_4S(CH_2)_7-$
144	$CH_3Z(CH_2)_{10}-$	164	$CH_3(CH_2)_8O(CH_2)_3-$
145	$HZ(CH_2)_{11}-$	165	$CH_3(CH_2)_8S(CH_2)_3-$
146	$CH_3(CH_2)_5Y(CH_2)_5-$	166	$4-CH_3-C_6H_4(CH_2)_9-$
147	$CH_2=CH(CH_2)_{11}-$	167	$4-C_2H_5-C_6H_4(CH_2)_7-$
148	$CH_3(CH_2)_6Y(CH_2)_4-$	168	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
149	$CH_3(CH_2)_4Y(CH_2)_6-$	169	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
150	$CH_3(CH_2)_3Y(CH_2)_7-$	170	$4-C_2H_5-C_6H_4(CH_2)_8-$
151	$CH_3(CH_2)_2Y(CH_2)_8-$	171	$cyclo-C_6H_{11}(CH_2)_8-$
152	$CH_3CH_2Y(CH_2)_9-$	172	$cyclo-C_6H_{11}(CH_2)_9-$
153	$CH_3Y(CH_2)_{10}-$	173	$cyclo-C_6H_{11}(CH_2)_{10}-$
154	$C_6H_5O(CH_2)_9-$	174	$C_6H_5(CH_2)_8-$
155	$C_6H_5S(CH_2)_9-$	175	$C_6H_5(CH_2)_9-$
156	$CH_3(CH_2)_7O(CH_2)_4-$	176	$C_6H_5(CH_2)_{10}-$
157	$CH_3(CH_2)_7S(CH_2)_4-$	177	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

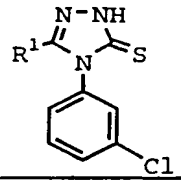


Example No.	R^1	Example No.	R^1
178	$CH_3(CH_2)_6Z(CH_2)_4-$	198	$CH_3(CH_2)_6O(CH_2)_5-$
179	$CH_3(CH_2)_5Z(CH_2)_5-$	199	$CH_3(CH_2)_6S(CH_2)_5-$
180	$CH_3(CH_2)_4Z(CH_2)_6-$	200	$CH_3(CH_2)_5O(CH_2)_6-$
181	$CH_3(CH_2)_3Z(CH_2)_7-$	201	$CH_3(CH_2)_5S(CH_2)_6-$
182	$CH_3(CH_2)_2Z(CH_2)_8-$	202	$CH_3(CH_2)_4O(CH_2)_7-$
183	$CH_3CH_2Z(CH_2)_9-$	203	$CH_3(CH_2)_4S(CH_2)_7-$
184	$CH_3Z(CH_2)_{10}-$	204	$CH_3(CH_2)_8O(CH_2)_3-$
185	$HZ(CH_2)_{11}-$	205	$CH_3(CH_2)_8S(CH_2)_3-$
186	$CH_3(CH_2)_5Y(CH_2)_5-$	206	$4-CH_3-C_6H_4(CH_2)_9-$
187	$CH_2=CH(CH_2)_{11}-$	207	$4-C_2H_5-C_6H_4(CH_2)_7-$
188	$CH_3(CH_2)_6Y(CH_2)_4-$	208	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
189	$CH_3(CH_2)_4Y(CH_2)_6-$	209	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
190	$CH_3(CH_2)_3Y(CH_2)_7-$	210	$4-C_2H_5-C_6H_4(CH_2)_8-$
191	$CH_3(CH_2)_2Y(CH_2)_8-$	211	$cyclo-C_6H_{11}(CH_2)_8-$
192	$CH_3CH_2Y(CH_2)_9-$	212	$cyclo-C_6H_{11}(CH_2)_9-$
193	$CH_3Y(CH_2)_{10}-$	213	$cyclo-C_6H_{11}(CH_2)_{10}-$
194	$C_6H_5O(CH_2)_9-$	214	$C_6H_5(CH_2)_8-$
195	$C_6H_5S(CH_2)_9-$	215	$C_6H_5(CH_2)_9-$
196	$CH_3(CH_2)_7O(CH_2)_4-$	216	$C_6H_5(CH_2)_{10}-$

BNSDOCID: <WO___9914204A1_I_>

197 $CH_3(CH_2)_7S(CH_2)_4$- 217 $C_6H_5(CH_2)_{11}$-

TABLE 3 (continued)

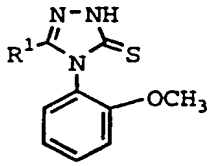


Example No.	R^1	Example No.	R^1
218	$CH_3(CH_2)_6Z(CH_2)_4$-	238	$CH_3(CH_2)_6O(CH_2)_5$-
219	$CH_3(CH_2)_5Z(CH_2)_5$-	239	$CH_3(CH_2)_6S(CH_2)_5$-
220	$CH_3(CH_2)_4Z(CH_2)_6$-	240	$CH_3(CH_2)_5O(CH_2)_6$-
221	$CH_3(CH_2)_3Z(CH_2)_7$-	241	$CH_3(CH_2)_5S(CH_2)_6$-
222	$CH_3(CH_2)_2Z(CH_2)_8$-	242	$CH_3(CH_2)_4O(CH_2)_7$-
223	$CH_3CH_2Z(CH_2)_9$-	243	$CH_3(CH_2)_4S(CH_2)_7$-
224	$CH_3Z(CH_2)_{10}$-	244	$CH_3(CH_2)_8O(CH_2)_3$-
225	$HZ(CH_2)_{11}$-	245	$CH_3(CH_2)_8S(CH_2)_3$-
226	$CH_3(CH_2)_5Y(CH_2)_5$-	246	$4\text{-}CH_3\text{-}C_6H_4(CH_2)_9$-
227	$CH_2{=}CH(CH_2)_{11}$-	247	$4\text{-}C_2H_5\text{-}C_6H_4(CH_2)_7$-
228	$CH_3(CH_2)_6Y(CH_2)_4$-	248	$4\text{-}(n\text{-}C_3H_7)C_6H_4(CH_2)_6$-
229	$CH_3(CH_2)_4Y(CH_2)_6$-	249	$4\text{-}(n\text{-}C_4H_9)C_6H_4(CH_2)_5$-
230	$CH_3(CH_2)_3Y(CH_2)_7$-	250	$4\text{-}C_2H_5\text{-}C_6H_4(CH_2)_8$-
231	$CH_3(CH_2)_2Y(CH_2)_8$-	251	$cyclo\text{-}C_6H_{11}(CH_2)_8$-
232	$CH_3CH_2Y(CH_2)_9$-	252	$cyclo\text{-}C_6H_{11}(CH_2)_9$-
233	$CH_3Y(CH_2)_{10}$-	253	$cyclo\text{-}C_6H_{11}(CH_2)_{10}$-
234	$C_6H_5O(CH_2)_9$-	254	$C_6H_5(CH_2)_8$-
235	$C_6H_5S(CH_2)_9$-	255	$C_6H_5(CH_2)_9$-

BNSDOCID: <WO 9914204A1 I >

236	$CH_3(CH_2)_7O(CH_2)_4$-	256	$C_6H_5(CH_2)_{10}$-
237	$CH_3(CH_2)_7S(CH_2)_4$-	257	$C_6H_5(CH_2)_{11}$-

TABLE 3 (continued)

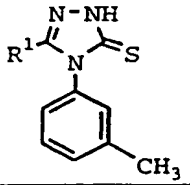


Example No.	R^1	Example No.	R^1
258	$CH_3(CH_2)_6Z(CH_2)_4$-	278	$CH_3(CH_2)_6O(CH_2)_5$-
259	$CH_3(CH_2)_5Z(CH_2)_5$-	279	$CH_3(CH_2)_6S(CH_2)_5$-
260	$CH_3(CH_2)_4Z(CH_2)_6$-	280	$CH_3(CH_2)_5O(CH_2)_6$-
261	$CH_3(CH_2)_3Z(CH_2)_7$-	281	$CH_3(CH_2)_5S(CH_2)_6$-
262	$CH_3(CH_2)_2Z(CH_2)_8$-	282	$CH_3(CH_2)_4O(CH_2)_7$-
263	$CH_3CH_2Z(CH_2)_9$-	283	$CH_3(CH_2)_4S(CH_2)_7$-
264	$CH_3Z(CH_2)_{10}$-	284	$CH_3(CH_2)_8O(CH_2)_3$-
265	$HZ(CH_2)_{11}$-	285	$CH_3(CH_2)_8S(CH_2)_3$-
266	$CH_3(CH_2)_5Y(CH_2)_5$-	286	4-CH_3-$C_6H_4(CH_2)_9$-
267	CH_2=$CH(CH_2)_{11}$-	287	4-C_2H_5-$C_6H_4(CH_2)_7$-
268	$CH_3(CH_2)_6Y(CH_2)_4$-	288	4-(n-C_3H_7)$C_6H_4(CH_2)_6$-
269	$CH_3(CH_2)_4Y(CH_2)_6$-	289	4-(n-C_4H_9)$C_6H_4(CH_2)_5$-
270	$CH_3(CH_2)_3Y(CH_2)_7$-	290	4-C_2H_5-$C_6H_4(CH_2)_8$-
271	$CH_3(CH_2)_2Y(CH_2)_8$-	291	cyclo-$C_6H_{11}(CH_2)_8$-
272	$CH_3CH_2Y(CH_2)_9$-	292	cyclo-$C_6H_{11}(CH_2)_9$-
273	$CH_3Y(CH_2)_{10}$-	293	cyclo-$C_6H_{11}(CH_2)_{10}$-
274	$C_6H_5O(CH_2)_9$-	294	$C_6H_5(CH_2)_8$-

BNSDOCID: <WO___9914204A1_I_>

275	$C_6H_5S(CH_2)_9$-	295	$C_6H_5(CH_2)_9$-
276	$CH_3(CH_2)_7O(CH_2)_4$-	296	$C_6H_5(CH_2)_{10}$-
277	$CH_3(CH_2)_7S(CH_2)_4$-	297	$C_6H_5(CH_2)_{11}$-

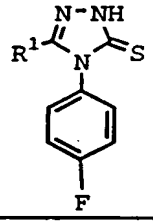
TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
298	$CH_3(CH_2)_6Z(CH_2)_4$-	318	$CH_3(CH_2)_6O(CH_2)_5$-
299	$CH_3(CH_2)_5Z(CH_2)_5$-	319	$CH_3(CH_2)_6S(CH_2)_5$-
300	$CH_3(CH_2)_4Z(CH_2)_6$-	320	$CH_3(CH_2)_5O(CH_2)_6$-
301	$CH_3(CH_2)_3Z(CH_2)_7$-	321	$CH_3(CH_2)_5S(CH_2)_6$-
302	$CH_3(CH_2)_2Z(CH_2)_8$-	322	$CH_3(CH_2)_4O(CH_2)_7$-
303	$CH_3CH_2Z(CH_2)_9$-	323	$CH_3(CH_2)_4S(CH_2)_7$-
304	$CH_3Z(CH_2)_{10}$-	324	$CH_3(CH_2)_8O(CH_2)_3$-
305	$HZ(CH_2)_{11}$-	325	$CH_3(CH_2)_8S(CH_2)_3$-
306	$CH_3(CH_2)_5Y(CH_2)_5$-	326	$4\text{-}CH_3\text{-}C_6H_4(CH_2)_9$-
307	$CH_2=CH(CH_2)_{11}$-	327	$4\text{-}C_2H_5\text{-}C_6H_4(CH_2)_7$-
308	$CH_3(CH_2)_6Y(CH_2)_4$-	328	$4\text{-}(n\text{-}C_3H_7)C_6H_4(CH_2)_6$-
309	$CH_3(CH_2)_4Y(CH_2)_6$-	329	$4\text{-}(n\text{-}C_4H_9)C_6H_4(CH_2)_5$-
310	$CH_3(CH_2)_3Y(CH_2)_7$-	330	$4\text{-}C_2H_5\text{-}C_6H_4(CH_2)_8$-
311	$CH_3(CH_2)_2Y(CH_2)_8$-	331	$cyclo\text{-}C_6H_{11}(CH_2)_8$-
312	$CH_3CH_2Y(CH_2)_9$-	332	$cyclo\text{-}C_6H_{11}(CH_2)_9$-
313	$CH_3Y(CH_2)_{10}$-	333	$cyclo\text{-}C_6H_{11}(CH_2)_{10}$-

314	$C_6H_5O(CH_2)_9$-	334	$C_6H_5(CH_2)_8$-
315	$C_6H_5S(CH_2)_9$-	335	$C_6H_5(CH_2)_9$-
316	$CH_3(CH_2)_7O(CH_2)_4$-	336	$C_6H_5(CH_2)_{10}$-
317	$CH_3(CH_2)_7S(CH_2)_4$-	337	$C_6H_5(CH_2)_{11}$-

TABLE 3 (continued)

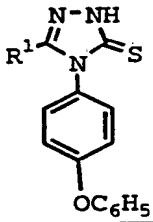


Example No.	R^1	Example No.	R^1
338	$CH_3(CH_2)_6Z(CH_2)_4$-	358	$CH_3(CH_2)_6O(CH_2)_5$-
339	$CH_3(CH_2)_5Z(CH_2)_5$-	359	$CH_3(CH_2)_6S(CH_2)_5$-
340	$CH_3(CH_2)_4Z(CH_2)_6$-	360	$CH_3(CH_2)_5O(CH_2)_6$-
341	$CH_3(CH_2)_3Z(CH_2)_7$-	361	$CH_3(CH_2)_5S(CH_2)_6$-
342	$CH_3(CH_2)_2Z(CH_2)_8$-	362	$CH_3(CH_2)_4O(CH_2)_7$-
343	$CH_3CH_2Z(CH_2)_9$-	363	$CH_3(CH_2)_4S(CH_2)_7$-
344	$CH_3Z(CH_2)_{10}$-	364	$CH_3(CH_2)_8O(CH_2)_3$-
345	$HZ(CH_2)_{11}$-	365	$CH_3(CH_2)_8S(CH_2)_3$-
346	$CH_3(CH_2)_5Y(CH_2)_5$-	366	4-CH_3-$C_6H_4(CH_2)_9$-
347	CH_2=CH$(CH_2)_{11}$-	367	4-C_2H_5-$C_6H_4(CH_2)_7$-
348	$CH_3(CH_2)_6Y(CH_2)_4$-	368	4-(n-C_3H_7)$C_6H_4(CH_2)_6$-
349	$CH_3(CH_2)_4Y(CH_2)_6$-	369	4-(n-C_4H_9)$C_6H_4(CH_2)_5$-
350	$CH_3(CH_2)_3Y(CH_2)_7$-	370	4-C_2H_5-$C_6H_4(CH_2)_8$-
351	$CH_3(CH_2)_2Y(CH_2)_8$-	371	cyclo-$C_6H_{11}(CH_2)_8$-

BNSDOCID: <WO___9914204A1_I_>

	352	$CH_3CH_2Y(CH_2)_9-$	372	cyclo-$C_6H_{11}(CH_2)_9-$
	353	$CH_3Y(CH_2)_{10}-$	373	cyclo-$C_6H_{11}(CH_2)_{10}-$
	354	$C_6H_5O(CH_2)_9-$	374	$C_6H_5(CH_2)_8-$
	355	$C_6H_5S(CH_2)_9-$	375	$C_6H_5(CH_2)_9-$
5	356	$CH_3(CH_2)_7O(CH_2)_4-$	376	$C_6H_5(CH_2)_{10}-$
	357	$CH_3(CH_2)_7S(CH_2)_4-$	377	$C_6H_5(CH_2)_{11}-$

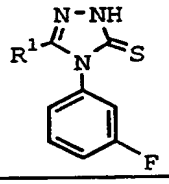
TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
378	$CH_3(CH_2)_6Z(CH_2)_4-$	398	$CH_3(CH_2)_6O(CH_2)_5-$
379	$CH_3(CH_2)_5Z(CH_2)_5-$	399	$CH_3(CH_2)_6S(CH_2)_5-$
380	$CH_3(CH_2)_4Z(CH_2)_6-$	400	$CH_3(CH_2)_5O(CH_2)_6-$
381	$CH_3(CH_2)_3Z(CH_2)_7-$	401	$CH_3(CH_2)_5S(CH_2)_6-$
382	$CH_3(CH_2)_2Z(CH_2)_8-$	402	$CH_3(CH_2)_4O(CH_2)_7-$
383	$CH_3CH_2Z(CH_2)_9-$	403	$CH_3(CH_2)_4S(CH_2)_7-$
384	$CH_3Z(CH_2)_{10}-$	404	$CH_3(CH_2)_8O(CH_2)_3-$
385	$HZ(CH_2)_{11}-$	405	$CH_3(CH_2)_8S(CH_2)_3-$
386	$CH_3(CH_2)_5Y(CH_2)_5-$	406	4-CH_3-$C_6H_4(CH_2)_9-$
387	$CH_2=CH(CH_2)_{11}-$	407	4-C_2H_5-$C_6H_4(CH_2)_7-$
388	$CH_3(CH_2)_6Y(CH_2)_4-$	408	4-(n-C_3H_7)$C_6H_4(CH_2)_6-$
389	$CH_3(CH_2)_4Y(CH_2)_6-$	409	4-(n-C_4H_9)$C_6H_4(CH_2)_5-$

390	$CH_3(CH_2)_3Y(CH_2)_7-$	410	$4-C_2H_5-C_6H_4(CH_2)_8-$
391	$CH_3(CH_2)_2Y(CH_2)_8-$	411	$cyclo-C_6H_{11}(CH_2)_8-$
392	$CH_3CH_2Y(CH_2)_9-$	412	$cyclo-C_6H_{11}(CH_2)_9-$
393	$CH_3Y(CH_2)_{10}-$	413	$cyclo-C_6H_{11}(CH_2)_{10}-$
394	$C_6H_5O(CH_2)_9-$	414	$C_6H_5(CH_2)_8-$
395	$C_6H_5S(CH_2)_9-$	415	$C_6H_5(CH_2)_9-$
396	$CH_3(CH_2)_7O(CH_2)_4-$	416	$C_6H_5(CH_2)_{10}-$
397	$CH_3(CH_2)_7S(CH_2)_4-$	417	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

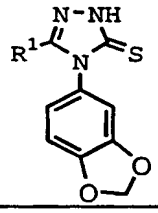


Example No.	R^1	Example No.	R^1
418	$CH_3(CH_2)_6Z(CH_2)_4-$	438	$CH_3(CH_2)_6O(CH_2)_5-$
419	$CH_3(CH_2)_5Z(CH_2)_5-$	439	$CH_3(CH_2)_6S(CH_2)_5-$
420	$CH_3(CH_2)_4Z(CH_2)_6-$	440	$CH_3(CH_2)_5O(CH_2)_6-$
421	$CH_3(CH_2)_3Z(CH_2)_7-$	441	$CH_3(CH_2)_5S(CH_2)_6-$
422	$CH_3(CH_2)_2Z(CH_2)_8-$	442	$CH_3(CH_2)_4O(CH_2)_7-$
423	$CH_3CH_2Z(CH_2)_9-$	443	$CH_3(CH_2)_4S(CH_2)_7-$
424	$CH_3Z(CH_2)_{10}-$	444	$CH_3(CH_2)_8O(CH_2)_3-$
425	$HZ(CH_2)_{11}-$	445	$CH_3(CH_2)_8S(CH_2)_3-$
426	$CH_3(CH_2)_5Y(CH_2)_5-$	446	$4-CH_3-C_6H_4(CH_2)_9-$
427	$CH_2=CH(CH_2)_{11}-$	447	$4-C_2H_5-C_6H_4(CH_2)_7-$
428	$CH_3(CH_2)_6Y(CH_2)_4-$	448	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$

ENSDOCID:<WO 9914204A1 | >

429	$CH_3(CH_2)_4Y(CH_2)_6-$	449	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
430	$CH_3(CH_2)_3Y(CH_2)_7-$	450	$4-C_2H_5-C_6H_4(CH_2)_8-$
431	$CH_3(CH_2)_2Y(CH_2)_8-$	451	$cyclo-C_6H_{11}(CH_2)_8-$
432	$CH_3CH_2Y(CH_2)_9-$	452	$cyclo-C_6H_{11}(CH_2)_9-$
433	$CH_3Y(CH_2)_{10}-$	453	$cyclo-C_6H_{11}(CH_2)_{10}-$
434	$C_6H_5O(CH_2)_9-$	454	$C_6H_5(CH_2)_8-$
435	$C_6H_5S(CH_2)_9-$	455	$C_6H_5(CH_2)_9-$
436	$CH_3(CH_2)_7O(CH_2)_4-$	456	$C_6H_5(CH_2)_{10}-$
437	$CH_3(CH_2)_7S(CH_2)_4-$	457	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

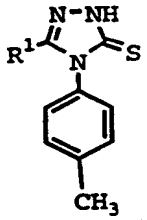


Example No.	R^1	Example No.	R^1
458	$CH_3(CH_2)_6Z(CH_2)_4-$	478	$CH_3(CH_2)_6O(CH_2)_5-$
459	$CH_3(CH_2)_5Z(CH_2)_5-$	479	$CH_3(CH_2)_6S(CH_2)_5-$
460	$CH_3(CH_2)_4Z(CH_2)_6-$	480	$CH_3(CH_2)_5O(CH_2)_6-$
461	$CH_3(CH_2)_3Z(CH_2)_7-$	481	$CH_3(CH_2)_5S(CH_2)_6-$
462	$CH_3(CH_2)_2Z(CH_2)_8-$	482	$CH_3(CH_2)_4O(CH_2)_7-$
463	$CH_3CH_2Z(CH_2)_9-$	483	$CH_3(CH_2)_4S(CH_2)_7-$
464	$CH_3Z(CH_2)_{10}-$	484	$CH_3(CH_2)_8O(CH_2)_3-$
465	$HZ(CH_2)_{11}-$	485	$CH_3(CH_2)_8S(CH_2)_3-$
466	$CH_3(CH_2)_5Y(CH_2)_5-$	486	$4-CH_3-C_6H_4(CH_2)_9-$

BNSDOCID: <WO 9914204A1 >

	467	$CH_2=CH(CH_2)_{11}-$	487	$4-C_2H_5-C_6H_4(CH_2)_7-$
	468	$CH_3(CH_2)_6Y(CH_2)_4-$	488	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
	469	$CH_3(CH_2)_4Y(CH_2)_6-$	489	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
	470	$CH_3(CH_2)_3Y(CH_2)_7-$	490	$4-C_2H_5-C_6H_4(CH_2)_8-$
	471	$CH_3(CH_2)_2Y(CH_2)_8-$	491	$cyclo-C_6H_{11}(CH_2)_8-$
	472	$CH_3CH_2Y(CH_2)_9-$	492	$cyclo-C_6H_{11}(CH_2)_9-$
	473	$CH_3Y(CH_2)_{10}-$	493	$cyclo-C_6H_{11}(CH_2)_{10}-$
	474	$C_6H_5O(CH_2)_9-$	494	$C_6H_5(CH_2)_8-$
	475	$C_6H_5S(CH_2)_9-$	495	$C_6H_5(CH_2)_9-$
	476	$CH_3(CH_2)_7O(CH_2)_4-$	496	$C_6H_5(CH_2)_{10}-$
	477	$CH_3(CH_2)_7S(CH_2)_4-$	497	$C_6H_5(CH_2)_{11}-$

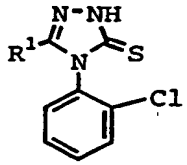
TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
498	$CH_3(CH_2)_6Z(CH_2)_4-$	518	$CH_3(CH_2)_6O(CH_2)_5-$
499	$CH_3(CH_2)_5Z(CH_2)_5-$	519	$CH_3(CH_2)_6S(CH_2)_5-$
500	$CH_3(CH_2)_4Z(CH_2)_6-$	520	$CH_3(CH_2)_5O(CH_2)_6-$
501	$CH_3(CH_2)_3Z(CH_2)_7-$	521	$CH_3(CH_2)_5S(CH_2)_6-$
502	$CH_3(CH_2)_2Z(CH_2)_8-$	522	$CH_3(CH_2)_4O(CH_2)_7-$
503	$CH_3CH_2Z(CH_2)_9-$	523	$CH_3(CH_2)_4S(CH_2)_7-$
504	$CH_3Z(CH_2)_{10}-$	524	$CH_3(CH_2)_8O(CH_2)_3-$

505	$HZ(CH_2)_{11}-$	525	$CH_3(CH_2)_8S(CH_2)_3-$
506	$CH_3(CH_2)_5Y(CH_2)_5-$	526	$4-CH_3-C_6H_4(CH_2)_9-$
507	$CH_2=CH(CH_2)_{11}-$	527	$4-C_2H_5-C_6H_4(CH_2)_7-$
508	$CH_3(CH_2)_6Y(CH_2)_4-$	528	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
509	$CH_3(CH_2)_4Y(CH_2)_6-$	529	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
510	$CH_3(CH_2)_3Y(CH_2)_7-$	530	$4-C_2H_5-C_6H_4(CH_2)_8-$
511	$CH_3(CH_2)_2Y(CH_2)_8-$	531	$cyclo-C_6H_{11}(CH_2)_8-$
512	$CH_3CH_2Y(CH_2)_9-$	532	$cyclo-C_6H_{11}(CH_2)_9-$
513	$CH_3Y(CH_2)_{10}-$	533	$cyclo-C_6H_{11}(CH_2)_{10}-$
514	$C_6H_5O(CH_2)_9-$	534	$C_6H_5(CH_2)_8-$
515	$C_6H_5S(CH_2)_9-$	535	$C_6H_5(CH_2)_9-$
516	$CH_3(CH_2)_7O(CH_2)_4-$	536	$C_6H_5(CH_2)_{10}-$
517	$CH_3(CH_2)_7S(CH_2)_4-$	537	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

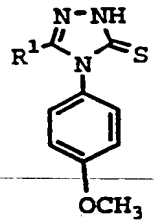


Example No.	R^1	Example No.	R^1
538	$CH_3(CH_2)_6Z(CH_2)_4-$	558	$CH_3(CH_2)_6O(CH_2)_5-$
539	$CH_3(CH_2)_5Z(CH_2)_5-$	559	$CH_3(CH_2)_6S(CH_2)_5-$
540	$CH_3(CH_2)_4Z(CH_2)_6-$	560	$CH_3(CH_2)_5O(CH_2)_6-$
541	$CH_3(CH_2)_3Z(CH_2)_7-$	561	$CH_3(CH_2)_5S(CH_2)_6-$
542	$CH_3(CH_2)_2Z(CH_2)_8-$	562	$CH_3(CH_2)_4O(CH_2)_7-$
543	$CH_3CH_2Z(CH_2)_9-$	563	$CH_3(CH_2)_4S(CH_2)_7-$

BNSDOCID: <WO 9914204A1 >

	544	$CH_3Z(CH_2)_{10}-$	564	$CH_3(CH_2)_8O(CH_2)_3-$
	545	$HZ(CH_2)_{11}-$	565	$CH_3(CH_2)_8S(CH_2)_3-$
	546	$CH_3(CH_2)_5Y(CH_2)_5-$	566	$4-CH_3-C_6H_4(CH_2)_9-$
	547	$CH_2=CH(CH_2)_{11}-$	567	$4-C_2H_5-C_6H_4(CH_2)_7-$
	548	$CH_3(CH_2)_6Y(CH_2)_4-$	568	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
	549	$CH_3(CH_2)_4Y(CH_2)_6-$	569	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
	550	$CH_3(CH_2)_3Y(CH_2)_7-$	570	$4-C_2H_5-C_6H_4(CH_2)_8-$
	551	$CH_3(CH_2)_2Y(CH_2)_8-$	571	$cyclo-C_6H_{11}(CH_2)_8-$
	552	$CH_3CH_2Y(CH_2)_9-$	572	$cyclo-C_6H_{11}(CH_2)_9-$
	553	$CH_3Y(CH_2)_{10}-$	573	$cyclo-C_6H_{11}(CH_2)_{10}-$
	554	$C_6H_5O(CH_2)_9-$	574	$C_6H_5(CH_2)_8-$
	555	$C_6H_5S(CH_2)_9-$	575	$C_6H_5(CH_2)_9-$
	556	$CH_3(CH_2)_7O(CH_2)_4-$	576	$C_6H_5(CH_2)_{10}-$
	557	$CH_3(CH_2)_7S(CH_2)_4-$	577	$C_6H_5(CH_2)_{11}-$

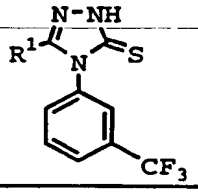
TABLE 3 (continued)



Example No.	R^1	Example No.	R^1
578	$CH_3(CH_2)_6Z(CH_2)_4-$	598	$CH_3(CH_2)_6O(CH_2)_5-$
579	$CH_3(CH_2)_5Z(CH_2)_5-$	599	$CH_3(CH_2)_6S(CH_2)_5-$
580	$CH_3(CH_2)_4Z(CH_2)_6-$	600	$CH_3(CH_2)_5O(CH_2)_6-$
581	$CH_3(CH_2)_3Z(CH_2)_7-$	601	$CH_3(CH_2)_5S(CH_2)_6-$

582	$CH_3(CH_2)_2Z(CH_2)_8-$	602	$CH_3(CH_2)_4O(CH_2)_7-$
583	$CH_3CH_2Z(CH_2)_9-$	603	$CH_3(CH_2)_4S(CH_2)_7-$
584	$CH_3Z(CH_2)_{10}-$	604	$CH_3(CH_2)_8O(CH_2)_3-$
585	$HZ(CH_2)_{11}-$	605	$CH_3(CH_2)_8S(CH_2)_3-$
586	$CH_3(CH_2)_5Y(CH_2)_5-$	606	$4-CH_3-C_6H_4(CH_2)_9-$
587	$CH_2=CH(CH_2)_{11}-$	607	$4-C_2H_5-C_6H_4(CH_2)_7-$
588	$CH_3(CH_2)_6Y(CH_2)_4-$	608	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
589	$CH_3(CH_2)_4Y(CH_2)_6-$	609	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
590	$CH_3(CH_2)_3Y(CH_2)_7-$	610	$4-C_2H_5-C_6H_4(CH_2)_8-$
591	$CH_3(CH_2)_2Y(CH_2)_8-$	611	$cyclo-C_6H_{11}(CH_2)_8-$
592	$CH_3CH_2Y(CH_2)_9-$	612	$cyclo-C_6H_{11}(CH_2)_9-$
593	$CH_3Y(CH_2)_{10}-$	613	$cyclo-C_6H_{11}(CH_2)_{10}-$
594	$C_6H_5O(CH_2)_9-$	614	$C_6H_5(CH_2)_8-$
595	$C_6H_5S(CH_2)_9-$	615	$C_6H_5(CH_2)_9-$
596	$CH_3(CH_2)_7O(CH_2)_4-$	616	$C_6H_5(CH_2)_{10}-$
597	$CH_3(CH_2)_7S(CH_2)_4-$	617	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

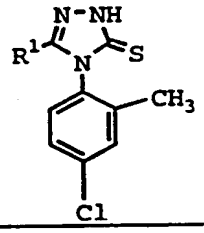


Example No.	R^1	Example No.	R^1
618	$CH_3(CH_2)_6Z(CH_2)_4-$	638	$CH_3(CH_2)_6O(CH_2)_5-$
619	$CH_3(CH_2)_5Z(CH_2)_5-$	639	$CH_3(CH_2)_6S(CH_2)_5-$
620	$CH_3(CH_2)_4Z(CH_2)_6-$	640	$CH_3(CH_2)_5O(CH_2)_6-$

BNSDOCID: <WO___9914204A1_I_>

	621	$CH_3(CH_2)_3Z(CH_2)_7-$	641	$CH_3(CH_2)_5S(CH_2)_6-$
	622	$CH_3(CH_2)_2Z(CH_2)_8-$	642	$CH_3(CH_2)_4O(CH_2)_7-$
	623	$CH_3CH_2Z(CH_2)_9-$	643	$CH_3(CH_2)_4S(CH_2)_7-$
	624	$CH_3Z(CH_2)_{10}-$	644	$CH_3(CH_2)_8O(CH_2)_3-$
	625	$HZ(CH_2)_{11}-$	645	$CH_3(CH_2)_8S(CH_2)_3-$
	626	$CH_3(CH_2)_5Y(CH_2)_5-$	646	$4-CH_3-C_6H_4(CH_2)_9-$
	627	$CH_2=CH(CH_2)_{11}-$	647	$4-C_2H_5-C_6H_4(CH_2)_7-$
	628	$CH_3(CH_2)_6Y(CH_2)_4-$	648	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
	629	$CH_3(CH_2)_4Y(CH_2)_6-$	649	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
	630	$CH_3(CH_2)_3Y(CH_2)_7-$	650	$4-C_2H_5-C_6H_4(CH_2)_8-$
	631	$CH_3(CH_2)_2Y(CH_2)_8-$	651	$cyclo-C_6H_{11}(CH_2)_8-$
	632	$CH_3CH_2Y(CH_2)_9-$	652	$cyclo-C_6H_{11}(CH_2)_9-$
	633	$CH_3Y(CH_2)_{10}-$	653	$cyclo-C_6H_{11}(CH_2)_{10}-$
	634	$C_6H_5O(CH_2)_9-$	654	$C_6H_5(CH_2)_8-$
	635	$C_6H_5S(CH_2)_9-$	655	$C_6H_5(CH_2)_9-$
	636	$CH_3(CH_2)_7O(CH_2)_4-$	656	$C_6H_5(CH_2)_{10}-$
	637	$CH_3(CH_2)_7S(CH_2)_4-$	657	$C_6H_5(CH_2)_{11}-$

TABLE 3 (continued)

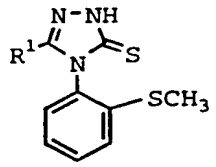


Example No.	R^1	Example No.	R^1
658	$CH_3(CH_2)_6Z(CH_2)_4-$	678	$CH_3(CH_2)_6O(CH_2)_5-$

659	$CH_3(CH_2)_5Z(CH_2)_5-$	679	$CH_3(CH_2)_6S(CH_2)_5-$
660	$CH_3(CH_2)_4Z(CH_2)_6-$	680	$CH_3(CH_2)_5O(CH_2)_6-$
661	$CH_3(CH_2)_3Z(CH_2)_7-$	681	$CH_3(CH_2)_5S(CH_2)_6-$
662	$CH_3(CH_2)_2Z(CH_2)_8-$	682	$CH_3(CH_2)_4O(CH_2)_7-$
663	$CH_3CH_2Z(CH_2)_9-$	683	$CH_3(CH_2)_4S(CH_2)_7-$
664	$CH_3Z(CH_2)_{10}-$	684	$CH_3(CH_2)_8O(CH_2)_3-$
665	$HZ(CH_2)_{11}-$	685	$CH_3(CH_2)_8S(CH_2)_3-$
666	$CH_3(CH_2)_5Y(CH_2)_5-$	686	$4-CH_3-C_6H_4(CH_2)_9-$
667	$CH_2=CH(CH_2)_{11}-$	687	$4-C_2H_5-C_6H_4(CH_2)_7-$
668	$CH_3(CH_2)_6Y(CH_2)_4-$	688	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
669	$CH_3(CH_2)_4Y(CH_2)_6-$	689	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
670	$CH_3(CH_2)_3Y(CH_2)_7-$	690	$4-C_2H_5-C_6H_4(CH_2)_8-$
671	$CH_3(CH_2)_2Y(CH_2)_8-$	691	$cyclo-C_6H_{11}(CH_2)_8-$
672	$CH_3CH_2Y(CH_2)_9-$	692	$cyclo-C_6H_{11}(CH_2)_9-$
673	$CH_3Y(CH_2)_{10}-$	693	$cyclo-C_6H_{11}(CH_2)_{10}-$
674	$C_6H_5O(CH_2)_9-$	694	$C_6H_5(CH_2)_8-$
675	$C_6H_5S(CH_2)_9-$	695	$C_6H_5(CH_2)_9-$
676	$CH_3(CH_2)_7O(CH_2)_4-$	696	$C_6H_5(CH_2)_{10}-$
677	$CH_3(CH_2)_7S(CH_2)_4-$	697	$C_6H_5(CH_2)_{11}-$

BNSDOCID: <WO 9914204A1 I >

TABLE 3 (continued)

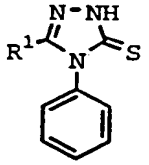


Example No.	R^1	Example No.	R^1
698	$CH_3(CH_2)_6Z(CH_2)_4-$	718	$CH_3(CH_2)_6O(CH_2)_5-$
699	$CH_3(CH_2)_5Z(CH_2)_5-$	719	$CH_3(CH_2)_6S(CH_2)_5-$
700	$CH_3(CH_2)_4Z(CH_2)_6-$	720	$CH_3(CH_2)_5O(CH_2)_6-$
701	$CH_3(CH_2)_3Z(CH_2)_7-$	721	$CH_3(CH_2)_5S(CH_2)_6-$
702	$CH_3(CH_2)_2Z(CH_2)_8-$	722	$CH_3(CH_2)_4O(CH_2)_7-$
703	$CH_3CH_2Z(CH_2)_9-$	723	$CH_3(CH_2)_4S(CH_2)_7-$
704	$CH_3Z(CH_2)_{10}-$	724	$CH_3(CH_2)_8O(CH_2)_3-$
705	$HZ(CH_2)_{11}-$	725	$CH_3(CH_2)_8S(CH_2)_3-$
706	$CH_3(CH_2)_5Y(CH_2)_5-$	726	$4-CH_3-C_6H_4(CH_2)_9-$
707	$CH_2=CH(CH_2)_{11}-$	727	$4-C_2H_5-C_6H_4(CH_2)_7-$
708	$CH_3(CH_2)_6Y(CH_2)_4-$	728	$4-(n-C_3H_7)C_6H_4(CH_2)_6-$
709	$CH_3(CH_2)_4Y(CH_2)_6-$	729	$4-(n-C_4H_9)C_6H_4(CH_2)_5-$
710	$CH_3(CH_2)_3Y(CH_2)_7-$	730	$4-C_2H_5-C_6H_4(CH_2)_8-$
711	$CH_3(CH_2)_2Y(CH_2)_8-$	731	$cyclo-C_6H_{11}(CH_2)_8-$
712	$CH_3CH_2Y(CH_2)_9-$	732	$cyclo-C_6H_{11}(CH_2)_9-$
713	$CH_3Y(CH_2)_{10}-$	733	$cyclo-C_6H_{11}(CH_2)_{10}-$
714	$C_6H_5O(CH_2)_9-$	734	$C_6H_5(CH_2)_8-$
715	$C_6H_5S(CH_2)_9-$	735	$C_6H_5(CH_2)_9-$

BNSDOCID: <WO 9914204A1_I_>

716	$CH_3(CH_2)_7O(CH_2)_4$-	736	$C_6H_5(CH_2)_{10}$-
717	$CH_3(CH_2)_7S(CH_2)_4$-	737	$C_6H_5(CH_2)_{11}$-

TABLE 3 (continued)

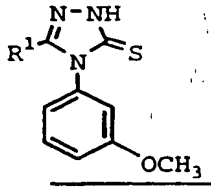


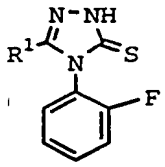
Example No.	R^1	Example No.	R^1
738	$CH_3(CH_2)_6Z(CH_2)_4$-	758	$CH_3(CH_2)_6O(CH_2)_5$-
739	$CH_3(CH_2)_5Z(CH_2)_5$-	759	$CH_3(CH_2)_6S(CH_2)_5$-
740	$CH_3(CH_2)_4Z(CH_2)_6$-	760	$CH_3(CH_2)_5O(CH_2)_6$-
741	$CH_3(CH_2)_3Z(CH_2)_7$-	761	$CH_3(CH_2)_5S(CH_2)_6$-
742	$CH_3(CH_2)_2Z(CH_2)_8$-	762	$CH_3(CH_2)_4O(CH_2)_7$-
743	$CH_3CH_2Z(CH_2)_9$-	763	$CH_3(CH_2)_4S(CH_2)_7$-
744	$CH_3Z(CH_2)_{10}$-	764	$CH_3(CH_2)_8O(CH_2)_3$-
745	$HZ(CH_2)_{11}$-	765	$CH_3(CH_2)_8S(CH_2)_3$-
746	$CH_3(CH_2)_5Y(CH_2)_5$-	766	4-CH_3-$C_6H_4(CH_2)_9$-
747	CH_2=$CH(CH_2)_{11}$-	767	4-C_2H_5-$C_6H_4(CH_2)_7$-
748	$CH_3(CH_2)_6Y(CH_2)_4$-	768	4-(n-C_3H_7)$C_6H_4(CH_2)_6$-
749	$CH_3(CH_2)_4Y(CH_2)_6$-	769	4-(n-C_4H_9)$C_6H_4(CH_2)_5$-
750	$CH_3(CH_2)_3Y(CH_2)_7$-	770	4-C_2H_5-$C_6H_4(CH_2)_8$-
751	$CH_3(CH_2)_2Y(CH_2)_8$-	771	cyclo-$C_6H_{11}(CH_2)_8$-
752	$CH_3CH_2Y(CH_2)_9$-	772	cyclo-$C_6H_{11}(CH_2)_9$-
753	$CH_3Y(CH_2)_{10}$-	773	cyclo-$C_6H_{11}(CH_2)_{10}$-
754	$C_6H_5O(CH_2)_9$-	774	$C_6H_5(CH_2)_8$-

755	$C_6H_5S(CH_2)_9-$	775	$C_6H_5(CH_2)_9-$
756	$CH_3(CH_2)_7O(CH_2)_4-$	776	$C_6H_5(CH_2)_{10}-$
757	$CH_3(CH_2)_7S(CH_2)_4-$	777	$C_6H_5(CH_2)_{11}-$

BNSDOCID: <WO___9914204A1_I_>

TABLE 4

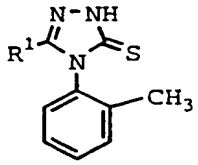


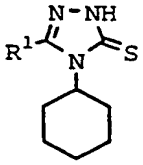


Example No.	R^1	Example No.	R^1
779	4-(n-$C_{10}H_{21}$)C_6H_4-	797	4-(n-$C_{10}H_{21}$)C_6H_4-
780	4-(n-C_9H_{19})C_6H_4-	798	4-(n-C_9H_{19})C_6H_4-
781	3-(n-$C_{10}H_{21}$)C_6H_4-	799	3-(n-$C_{10}H_{21}$)C_6H_4-
782	3-(n-C_9H_{19})C_6H_4-	800	3-(n-C_9H_{19})C_6H_4-
783	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	801	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
784	4-(n-C_9H_{19})$C_6H_4CH_2$-	802	4-(n-C_9H_{19})$C_6H_4CH_2$-
785	4-(n-C_7H_{15})$C_6H_4CH_2$-	803	4-(n-C_8H_{17})$C_6H_4CH_2$-
786	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	804	4-(n-C_7H_{15})$C_6H_4CH_2$-
787	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	805	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
788	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	806	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
789	4-(n-C_8H_{17})$C_6H_4OCH_2$-	807	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
790	4-(n-C_7H_{15})$C_6H_4OCH_2$-	808	4-(n-C_8H_{17})$C_6H_4OCH_2$-
791	4-(n-C_6H_{13})$C_6H_4OCH_2$-	809	4-(n-C_7H_{15})$C_6H_4OCH_2$-
792	3-(n-C_9H_{19})$C_6H_4CH_2$-	810	4-(n-C_6H_{13})$C_6H_4OCH_2$-
793	3-(n-C_8H_{17})$C_6H_4CH_2$-	811	3-(n-C_9H_{19})$C_6H_4CH_2$-
794	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	812	3-(n-C_8H_{17})$C_6H_4CH_2$-
795	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	813	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
796	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	814	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
		815	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO 9914204A1 I >

TABLE 4 (con't)

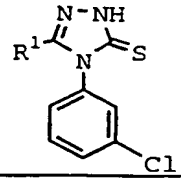


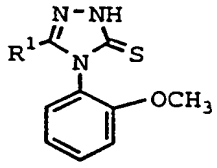


Example No.	R^1	Example No.	R^1
816	4-(n-$C_{10}H_{21}$)C_6H_4-	835	4-(n-$C_{10}H_{21}$)C_6H_4-
817	4-(n-C_9H_{19})C_6H_4-	836	4-(n-C_9H_{19})C_6H_4-
818	3-(n-$C_{10}H_{21}$)C_6H_4-	837	3-(n-$C_{10}H_{21}$)C_6H_4-
819	3-(n-C_9H_{19})C_6H_4-	838	3-(n-C_9H_{19})C_6H_4-
820	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	839	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
821	4-(n-C_9H_{19})$C_6H_4CH_2$-	840	4-(n-C_9H_{19})$C_6H_4CH_2$-
822	4-(n-C_8H_{17})$C_6H_4CH_2$-	841	4-(n-C_8H_{17})$C_6H_4CH_2$-
823	4-(n-C_7H_{15})$C_6H_4CH_2$-	842	4-(n-C_7H_{15})$C_6H_4CH_2$-
824	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	843	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
825	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	844	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
826	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	845	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
827	4-(n-C_8H_{17})$C_6H_4OCH_2$-	846	4-(n-C_8H_{17})$C_6H_4OCH_2$-
828	4-(n-C_7H_{15})$C_6H_4OCH_2$-	847	4-(n-C_7H_{15})$C_6H_4OCH_2$-
829	4-(n-C_6H_{13})$C_6H_4OCH_2$-	848	4-(n-C_6H_{13})$C_6H_4OCH_2$-
830	3-(n-C_9H_{19})$C_6H_4CH_2$-	849	3-(n-C_9H_{19})$C_6H_4CH_2$-
831	3-(n-C_8H_{17})$C_6H_4CH_2$-	850	3-(n-C_8H_{17})$C_6H_4CH_2$-
832	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	851	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
833	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	852	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
834	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	853	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

Table 4 (con't)

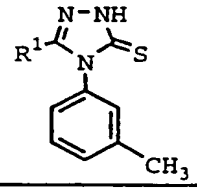


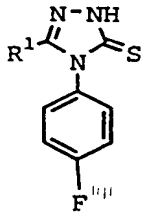


Example No.	R^1	Example No.	R^1
854	4-(n-$C_{10}H_{21}$)C_6H_4-	873	4-(n-$C_{10}H_{21}$)C_6H_4-
855	4-(n-C_9H_{19})C_6H_4-	874	4-(n-C_9H_{19})C_6H_4-
856	3-(n-$C_{10}H_{21}$)C_6H_4-	875	3-(n-$C_{10}H_{21}$)C_6H_4-
857	3-(n-C_9H_{19})C_6H_4-	876	3-(n-C_9H_{19})C_6H_4-
858	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	877	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
859	4-(n-C_9H_{19})$C_6H_4CH_2$-	878	4-(n-C_9H_{19})$C_6H_4CH_2$-
860	4-(n-C_8H_{17})$C_6H_4CH_2$-	879	4-(n-C_8H_{17})$C_6H_4CH_2$-
861	4-(n-C_7H_{15})$C_6H_4CH_2$-	880	4-(n-C_7H_{15})$C_6H_4CH_2$-
862	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	881	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
863	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	882	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
864	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	883	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
865	4-(n-C_8H_{17})$C_6H_4OCH_2$-	884	4-(n-C_8H_{17})$C_6H_4OCH_2$-
866	4-(n-C_7H_{15})$C_6H_4OCH_2$-	885	4-(n-C_7H_{15})$C_6H_4OCH_2$-
867	4-(n-C_6H_{13})$C_6H_4OCH_2$-	886	4-(n-C_6H_{13})$C_6H_4OCH_2$-
868	3-(n-C_9H_{19})$C_6H_4CH_2$-	887	3-(n-C_9H_{19})$C_6H_4CH_2$-
869	3-(n-C_8H_{17})$C_6H_4CH_2$-	888	3-(n-C_8H_{17})$C_6H_4CH_2$-
870	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	889	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
871	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	890	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
872	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	891	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO 9914204A1_I_>

TABLE 4 (con't)

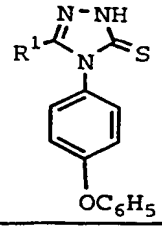


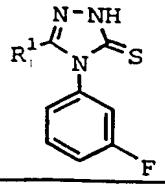


Example No.	R^1	Example No.	R^1
892	4-(n-$C_{10}H_{21}$)C_6H_4-	911	4-(n-$C_{10}H_{21}$)C_6H_4-
893	4-(n-C_9H_{19})C_6H_4-	912	4-(n-C_9H_{19})C_6H_4-
894	3-(n-$C_{10}H_{21}$)C_6H_4-	913	3-(n-$C_{10}H_{21}$)C_6H_4-
895	3-(n-C_9H_{19})C_6H_4-	914	3-(n-C_9H_{19})C_6H_4-
896	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	915	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
897	4-(n-C_9H_{19})$C_6H_4CH_2$-	916	4-(n-C_9H_{19})$C_6H_4CH_2$-
898	4-(n-C_8H_{17})$C_6H_4CH_2$-	917	4-(n-C_8H_{17})$C_6H_4CH_2$-
899	4-(n-C_7H_{15})$C_6H_4CH_2$-	918	4-(n-C_7H_{15})$C_6H_4CH_2$-
900	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	919	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
901	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	920	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
902	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	921	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
903	4-(n-C_8H_{17})$C_6H_4OCH_2$-	922	4-(n-C_8H_{17})$C_6H_4OCH_2$-
904	4-(n-C_7H_{15})$C_6H_4OCH_2$-	923	4-(n-C_7H_{15})$C_6H_4OCH_2$-
905	4-(n-C_6H_{13})$C_6H_4OCH_2$-	924	4-(n-C_6H_{13})$C_6H_4OCH_2$-
906	3-(n-C_9H_{19})$C_6H_4CH_2$-	925	3-(n-C_9H_{19})$C_6H_4CH_2$-
907	3-(n-C_8H_{17})$C_6H_4CH_2$-	926	3-(n-C_8H_{17})$C_6H_4CH_2$-
908	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	927	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
909	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	928	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
910	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	929	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

TABLE 4 (con't)

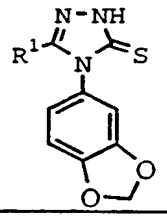


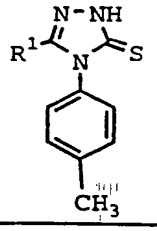


Example No.	R^1	Example No.	R^1
930	4-(n-$C_{10}H_{21}$)C_6H_4-	949	4-(n-$C_{10}H_{21}$)C_6H_4-
931	4-(n-C_9H_{19})C_6H_4-	950	4-(n-C_9H_{19})C_6H_4-
932	3-(n-$C_{10}H_{21}$)C_6H_4-	951	3-(n-$C_{10}H_{21}$)C_6H_4-
933	3-(n-C_9H_{19})C_6H_4-	952	3-(n-C_9H_{19})C_6H_4-
934	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	953	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
935	4-(n-C_9H_{19})$C_6H_4CH_2$-	954	4-(n-C_9H_{19})$C_6H_4CH_2$-
936	4-(n-C_8H_{17})$C_6H_4CH_2$-	955	4-(n-C_8H_{17})$C_6H_4CH_2$-
937	4-(n-C_7H_{15})$C_6H_4CH_2$-	956	4-(n-C_7H_{15})$C_6H_4CH_2$-
938	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	957	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
939	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	958	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
940	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	959	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
941	4-(n-C_8H_{17})$C_6H_4OCH_2$-	960	4-(n-C_8H_{17})$C_6H_4OCH_2$-
942	4-(n-C_7H_{15})$C_6H_4OCH_2$-	961	4-(n-C_7H_{15})$C_6H_4OCH_2$-
943	4-(n-C_6H_{13})$C_6H_4OCH_2$-	962	4-(n-C_6H_{13})$C_6H_4OCH_2$-
944	3-(n-C_9H_{19})$C_6H_4CH_2$-	963	3-(n-C_9H_{19})$C_6H_4CH_2$-
945	3-(n-C_8H_{17})$C_6H_4CH_2$-	964	3-(n-C_8H_{17})$C_6H_4CH_2$-
946	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	965	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
947	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	966	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
948	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	967	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

TABLE 4 (con't)

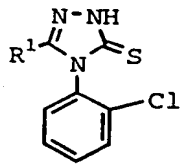


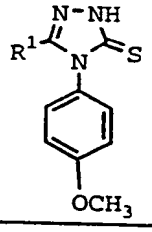


Example No.	R^1	Example No.	R^1
968	4-(n-$C_{10}H_{21}$)C_6H_4-	987	4-(n-$C_{10}H_{21}$)C_6H_4-
969	4-(n-C_9H_{19})C_6H_4-	988	4-(n-C_9H_{19})C_6H_4-
970	3-(n-$C_{10}H_{21}$)C_6H_4-	989	3-(n-$C_{10}H_{21}$)C_6H_4-
971	3-(n-C_9H_{19})C_6H_4-	990	3-(n-C_9H_{19})C_6H_4-
972	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	991	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
973	4-(n-C_9H_{19})$C_6H_4CH_2$-	992	4-(n-C_9H_{19})$C_6H_4CH_2$-
974	4-(n-C_8H_{17})$C_6H_4CH_2$-	993	4-(n-C_8H_{17})$C_6H_4CH_2$-
975	4-(n-C_7H_{15})$C_6H_4CH_2$-	994	4-(n-C_7H_{15})$C_6H_4CH_2$-
976	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	995	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
977	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	996	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
978	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	997	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
979	4-(n-C_8H_{17})$C_6H_4OCH_2$-	998	4-(n-C_8H_{17})$C_6H_4OCH_2$-
980	4-(n-C_7H_{15})$C_6H_4OCH_2$-	999	4-(n-C_7H_{15})$C_6H_4OCH_2$-
981	4-(n-C_6H_{13})$C_6H_4OCH_2$-	1000	4-(n-C_6H_{13})$C_6H_4OCH_2$-
982	3-(n-C_9H_{19})$C_6H_4CH_2$-	1001	3-(n-C_9H_{19})$C_6H_4CH_2$-
983	3-(n-C_8H_{17})$C_6H_4CH_2$-	1002	3-(n-C_8H_{17})$C_6H_4CH_2$-
984	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	1003	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
985	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	1004	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
986	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	1005	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

TABLE 4 (con't)

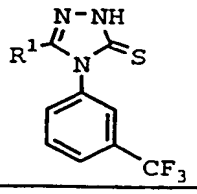


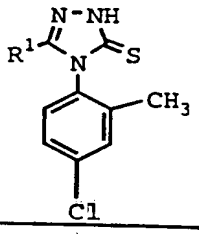


Example No.	R^1	Example No.	R^1
1006	4-(n-$C_{10}H_{21}$)C_6H_4-	1025	4-(n-$C_{10}H_{21}$)C_6H_4-
1007	4-(n-C_9H_{19})C_6H_4-	1026	4-(n-C_9H_{19})C_6H_4-
1008	3-(n-$C_{10}H_{21}$)C_6H_4-	1027	3-(n-$C_{10}H_{21}$)C_6H_4-
1009	3-(n-C_9H_{19})C_6H_4-	1028	3-(n-C_9H_{19})C_6H_4-
1010	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	1029	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
1011	4-(n-C_9H_{19})$C_6H_4CH_2$-	1030	4-(n-C_9H_{19})$C_6H_4CH_2$-
1012	4-(n-C_8H_{17})$C_6H_4CH_2$-	1031	4-(n-C_8H_{17})$C_6H_4CH_2$-
1013	4-(n-C_7H_{15})$C_6H_4CH_2$-	1032	4-(n-C_7H_{15})$C_6H_4CH_2$-
1014	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	1033	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
1015	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	1034	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
1016	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	1035	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
1017	4-(n-C_8H_{17})$C_6H_4OCH_2$-	1036	4-(n-C_8H_{17})$C_6H_4OCH_2$-
1018	4-(n-C_7H_{15})$C_6H_4OCH_2$-	1037	4-(n-C_7H_{15})$C_6H_4OCH_2$-
1019	4-(n-C_6H_{13})$C_6H_4OCH_2$-	1038	4-(n-C_6H_{13})$C_6H_4OCH_2$-
1020	3-(n-C_9H_{19})$C_6H_4CH_2$-	1039	3-(n-C_9H_{19})$C_6H_4CH_2$-
1021	3-(n-C_8H_{17})$C_6H_4CH_2$-	1040	3-(n-C_8H_{17})$C_6H_4CH_2$-
1022	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	1041	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
1023	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	1042	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
1024	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	1043	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

TABLE 4 (con't)

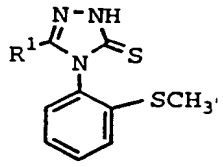


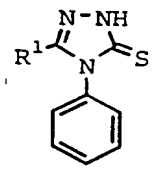


Example No.	R^1	Example No.	R^1
1044	4-(n-$C_{10}H_{21}$)C_6H_4-	1063	4-(n-$C_{10}H_{21}$)C_6H_4-
1045	4-(n-C_9H_{19})C_6H_4-	1064	4-(n-C_9H_{19})C_6H_4-
1046	3-(n-$C_{10}H_{21}$)C_6H_4-	1065	3-(n-$C_{10}H_{21}$)C_6H_4-
1047	3-(n-C_9H_{19})C_6H_4-	1066	3-(n-C_9H_{19})C_6H_4-
1048	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	1067	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
1049	4-(n-C_9H_{19})$C_6H_4CH_2$-	1068	4-(n-C_9H_{19})$C_6H_4CH_2$-
1050	4-(n-C_8H_{17})$C_6H_4CH_2$-	1069	4-(n-C_8H_{17})$C_6H_4CH_2$-
1051	4-(n-C_7H_{15})$C_6H_4CH_2$-	1070	4-(n-C_7H_{15})$C_6H_4CH_2$-
1052	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	1071	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
1053	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	1072	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
1054	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	1073	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
1055	4-(n-C_8H_{17})$C_6H_4OCH_2$-	1074	4-(n-C_8H_{17})$C_6H_4OCH_2$-
1056	4-(n-C_7H_{15})$C_6H_4OCH_2$-	1075	4-(n-C_7H_{15})$C_6H_4OCH_2$-
1057	4-(n-C_6H_{13})$C_6H_4OCH_2$-	1076	4-(n-C_6H_{13})$C_6H_4OCH_2$-
1058	3-(n-C_9H_{19})$C_6H_4CH_2$-	1077	3-(n-C_9H_{19})$C_6H_4CH_2$-
1059	3-(n-C_8H_{17})$C_6H_4CH_2$-	1078	3-(n-C_8H_{17})$C_6H_4CH_2$-
1060	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	1079	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
1061	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	1080	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
1062	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	1081	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

3NSDOCID: <WO___9914204A1_I_>

TABLE 4 (con't)

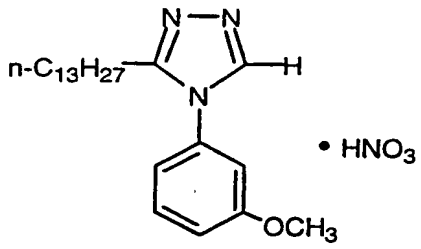




Example No.	R^1	Example No.	R^1
1082	4-(n-$C_{10}H_{21}$)C_6H_4-	1101	4-(n-$C_{10}H_{21}$)C_6H_4-
1083	4-(n-C_9H_{19})C_6H_4-	1102	4-(n-C_9H_{19})C_6H_4-
1084	3-(n-$C_{10}H_{21}$)C_6H_4-	1103	3-(n-$C_{10}H_{21}$)C_6H_4-
1085	3-(n-C_9H_{19})C_6H_4-	1104	3-(n-C_9H_{19})C_6H_4-
1086	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-	1105	4-(n-$C_{10}H_{21}$)$C_6H_4CH_2$-
1087	4-(n-C_9H_{19})$C_6H_4CH_2$-	1106	4-(n-C_9H_{19})$C_6H_4CH_2$-
1088	4-(n-C_8H_{17})$C_6H_4CH_2$-	1107	4-(n-C_8H_{17})$C_6H_4CH_2$-
1089	4-(n-C_7H_{15})$C_6H_4CH_2$-	1108	4-(n-C_7H_{15})$C_6H_4CH_2$-
1090	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-	1109	4-(n-$C_7H_{15}Z$)$C_6H_4CH_2$-
1091	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-	1110	4-(n-$C_6H_{13}Z$)$C_6H_4CH_2$-
1092	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-	1111	4-(n-$C_5H_{11}Z$)$C_6H_4CH_2$-
1093	4-(n-C_8H_{17})$C_6H_4OCH_2$-	1112	4-(n-C_8H_{17})$C_6H_4OCH_2$-
1094	4-(n-C_7H_{15})$C_6H_4OCH_2$-	1113	4-(n-C_7H_{15})$C_6H_4OCH_2$-
1095	4-(n-C_6H_{13})$C_6H_4OCH_2$-	1114	4-(n-C_6H_{13})$C_6H_4OCH_2$-
1096	3-(n-C_9H_{19})$C_6H_4CH_2$-	1115	3-(n-C_9H_{19})$C_6H_4CH_2$-
1097	3-(n-C_8H_{17})$C_6H_4CH_2$-	1116	3-(n-C_8H_{17})$C_6H_4CH_2$-
1098	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	1117	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-
1099	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	1118	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-
1100	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	1119	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-

BNSDOCID: <WO___9914204A1_I_>

EXAMPLE 1120



3-Tridecyl-4-(3-methoxyphenyl)-4H-1,2,4-triazole, nitrate

Following the general procedure adapted from C. Ainsworth, Organic Synthesis Collective Volume 5, 1070 (1973), concentrated nitric acid (0.6 mL) was dissolved in cold water (5.0 mL). Solid sodium nitrite (1 mg) was added, followed with solid 2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione (Example 1) (about 0.1 g). The resulting slurry was gently warmed to about 45-50 °C. The reaction gas was monitored for the evolution of a brown gas. The remaining triazol-3-thione (0.68 g) was added as a solid in portions so as to maintain the reaction. When the addition was complete, the reaction mixture was stirred at 45-50 °C for one hour then cooled to room temperature. As the reaction completed, the evolution of gas ceased and foaming diminished. Water (about 5 mL) was added to facilitate stirring. The mixture was stirred overnight at room temperature to produce a flocculent off-white precipitate, which was collected by vacuum filtration, washed with cold water and dried *in vacuo* to give 3-tridecyl-4-(3-methoxyphenyl)-4H-1,2,4-triazole, nitrate as an off-white solid: M.P. 65.4-68.9 °C. ^{1}H NMR (d_6-acetone) δ 0.85 (t, J = 6 Hz, 3H),

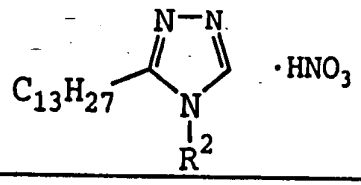
BNSDOCID: <WO___9914204A1_I_>

1.28 (br s, 20H), 1.72 (m, 2H), 3.02 (t, J = 8 Hz, 2H), 3.93 (s, 3H), 7.45 (m, 4H), 9.14 (s, 1H). Calc'd for $C_{22}H_{36}N_4O_4$: C, 62.82; H, 8.64; N, 13.32. Found: C, 63.04; H, 8.59; N, 13.11.

Additional representative examples of substituted-1,2,4-triazoles can be prepared by one skilled in the art from the appropriate triazole thiones using similar methods as shown in Example 1120 and can be found in Table 5 below.

RNSDOCID: <WO 9914204A1 >

TABLE 5

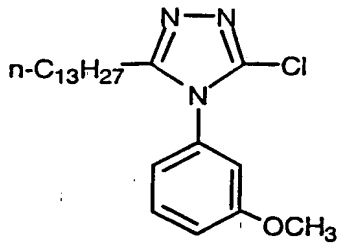


Example No.	R²	m.p.	Analyses
1121	3-CH_3-C_6H_4- •0.75H_2O	53-56	Calcd. C,63.21; H,9.04; N,13.40 Obs. C,63.34; H,9.15; N,12.94
1122	4-CH_3O-C_6H_4-	62-64	Calcd. C,62.82; H,8.64; N,13.32 Obs. C,62.80; H,8.63; N,13.27
1123	2-CH_3O-C_6H_4-	75-77	Calcd. C,62.82; H,8.64; N,13.32 Obs. C,62.47; H,8.33; N,12.80
1124	2-naphthyl-	65.2-66.2	Calcd. C,68.14; H,8.25; N,12.72 Obs. C,68.22; H,8.26; N,12.67
1125	3,4-(OCH_2O)-C_6H_3-	103-105	Calcd. C,60.84; H,7.89; N,12.92 Obs. C,61.48; H,8.17; N,13.01
1126	2-Cl-C_6H_4-	75.5-79.6	FABMS: m/z = 362 (M+H) HRMS: Calcd 362.2363 Found: 362.2345
1127	2-F-C_6H_4-	52.1-55.0	FABMS: m/z = 346 (M+H) HRMS: Calcd 346.2659 Found: 346.2662
1128	3-Cl-C_6H_4-	61.5-63.2	FABMS: m/z = 362 (M+H) HRMS: Calcd 362.2363 Found: 362.2336
1129	3-$C_6H_5CH_2O$-C_6H_4-	51.7-52.9	FABMS: m/z = 434 (M+H) HRMS: Calcd 434.3171 Found: 434.3193
1130	4-$C_6H_5CH_2O$-C_6H_4-	123.0-124.1	Calcd. C,67.72; H,8.13; N,11.28 Obs. C,67.97; H,8.15; N,11.23
1131	4-Cl-C_6H_4-	94.1-95.1	Calcd. C,59.34; H,7.84; N,13.18 Obs. C,59.29; H,7.93; N,13.10
1132	2-CH_3-C_6H_4-	57.8-61.7	Calcd. C,65.30; H,8.99; N,13.85 Obs. C,65.37; H,8.77; N,13.96

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9914204A1_I_>

EXAMPLE 1133



3-Chloro-4-(3-methoxyphenyl)-5-tridecyl-4H-1,2,4-triazole

Solid 2,4,-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione (Example 1) (0.20 g, 0.51 mmol) was dissolved in SO_2Cl_2 (10 mL) and stirred at room temperature for 45 minutes at which time TLC analysis showed that the reaction was complete. The reaction mixture was poured over ice (100 g), and ethyl acetate (400 mL) was used to extract the product. The organic layer was washed with water (25 mL), saturated sodium bicarbonate (2 x 25 mL), and brine (2 x 25 mL), then dried ($MgSO_4$) and concentrated to leave a clear oil. This oil was dissolved in hot hexane, and upon cooling, a white solid formed. This solid was collected by vacuum filtration, washed with n-pentane, and air-dried to give 70 mg (35%) of a white solid: m.p. 63.6-65.1 °C. Subsequent recrystallization from acetonitrile provided an analytical sample 2 mg (1%) of the desired 3-chloro-5-tridecyl-4-(3-methoxyphenyl)-4H-1,2,4-triazole product as a white solid: m.p. 65.3-67.3 °C. ^1H NMR (d_6-DMSO) δ7.50 (m, 1H), 7.15 (m, 2H),

BNSDOCID: <WO 9914204A1_I_>

7.04 (m, 1H), 3.78 (s, 3H), 2.52 (t, J = 7.5 Hz, 2H), 1.50 (m, 2H), 1.21 (m, 20H), 0.83 (t, J = 6.6 Hz, 3H). ESMS m/z= 392 (M+H). HRMS: Calc'd 392.2469; Observed 392.2454.

Biological Evaluation

WHOLE SERUM CETP ACTIVITY ASSAY (Tritiated cholesterol ester)

Blood was obtained from healthy volunteers recruited from the personnel of Monsanto Company, Saint Louis, MO. Blood was either collected in tubes containing EDTA (EDTA plasma pool) or without (spun to form the serum pool). The EDTA human plasma pool or human serum pool, previously stored at -20 °C, was thawed at room temperature, and centrifuged for 5 minutes to remove any particulate matter. Tritiated HDL, radiolabeled in the cholesteryl ester moiety ([^{3}H]CE-HDL) as described by Morton and Zilversmit (J. Biol. Chem., 256, 11992-95 (1981)), was added to the plasma or serum to a final concentration of (25 µg/ml cholesterol). Inhibitor compounds were added to the plasma or serum as follows: Equal volumes of the plasma or serum containing the [^{3}H]CE-HDL (396 µl) were pipetted into micro tubes (Titertube®, Bio-Rad Laboratories,Hercules, CA). Compounds, usually dissolved as 20-50 mM stock solutions in DMSO, were serially diluted in DMSO (or an alternative solvent in some cases, such as dimethylformamide or ethanol). Four µl of each of the serial dilutions of inhibitor compounds or DMSO alone were then added to each of the plasma or serum tubes. The tubes were immediately mixed. Triplicate aliquots (100 µl) from each plasma or

BNSDOCID: <WO__9914204A1_I_>

serum tube were then transferred to wells of 96-well round-bottomed polystyrene microtiter plates (Corning, Corning, NY). Plates were sealed with plastic film and incubated at 37 °C for 4 hours. Test wells contained plasma or serum with dilutions of inhibitor compounds. Control wells contained plasma or serum with DMSO alone. Blank wells contained plasma or serum with DMSO alone that were left in the micro tubes at 4 °C for the 4 hour incubation and were added to the microtiter wells at the end of the incubation period. VLDL and LDL were precipitated by the addition of 10 µl of precipitating reagent (1% (w/v) Dextran Sulfate (Dextralip50)/0.5M magnesium chloride, pH 7.4) to all wells. The wells were mixed on a plate mixer and then incubated at ambient temperature for 10 min. The plates were then centrifuged at 1000 x g for 30 mins at 10 °C. The supernatants (50 µl) from each well were then transferred to Picoplate™ 96 plate wells (Packard, Meriden, CT) containing 250:1 Microscint™-40 (Packard, Meriden, CT). The plates were heat-sealed (TopSeal™-P, Packard, Meriden, CT) according to the manufacturers directions and mixed for 30 min. Radioactivity was measured on a microplate scintillation counter (TopCount, Packard, Meriden, CT). IC_{50}'s were determined as the concentration of inhibitor compound inhibiting transfer of [^{3}H]CE from the supernatant [^{3}H]CE-HDL to the precipitated VLDL and LDL by 50% compared to the transfer obtained in the control wells. The maximum percent transfer (in the control wells) was determined using the following equation:

BNSDOCID: <WO 9914204A1 I >

$$\% \text{ Transfer} = \frac{[dpm_{blank} - dpm_{control}] \times 100}{dpm_{blank}}$$

The percent of control transfer determined in the wells containing inhibitor compounds was determined as follows:

$$\% \text{ Control} = \frac{[dpm_{blank} - dpm_{test}] \times 100}{dpm_{blank} - dpm_{control}}$$

IC_{50} values were then calculated from plots of % control versus concentration of inhibitor compound. Examples of IC_{50} values determined by this method are specified in Table 6.

CETP Activity *In Vitro*

The ability of compounds to inhibit CETP were assessed using an *in vitro* assay that measured the rate of transfer of radiolabled cholesteryl ester ([^{3}H]CE) from HDL donor particles to LDL acceptor particles. Details of the assay are provided by Glenn et al. ("Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B) Immunochemical Assay of CETP Protein," *Meth. Enzymol.*, Glenn and Melton (Meth. Enzymol., 263, 339-351 (1996)). CETP was obtained from the serum-free conditioned medium of CHO cells transfected with a cDNA for CETP (Wang, S. et al. *J. Biol Chem. 267*, 17487-17490 1992). To measure CETP activity, [^{3}H]CE-labeled HDL, LDL, CETP and assay buffer (50 mM tris(hydroxymethyl)aminomethane, pH 7.4; 150 mM sodium chloride; 2 mM ethylenediamine-tetraacetic acid; 1%

BNSDOCID: <WO___9914204A1_I_>

bovine serum albumin) were incubated in a volume of 200 µl, for 2 hours at 37°C in 96 well plates. LDL was differentially precipitated by the addition of 50 µl of 1% (w/v) dextran sulfate/0.5 M magnesium chloride, mixed by vortex, and incubated at room temperature for 10 minutes The solution (200µl) was transferred to a filter plate (Millipore). After filtration, the radioactivity present in the precipitated LDL was measured by liquid scintillation counting. Correction for non-specific transfer or precipitation was made by including samples that did not contain CETP. The rate of [^{3}H]CE transfer using this assay was linear with respect to time and CETP concentration, up to 25-30% of [^{3}H]CE transferred.

The potency of test compounds was determined by performing the above described assay in the presence of varying concentrations of the test compounds and determining the concentration required for 50% inhibition of transfer of [^{3}H]CE from HDL to LDL. This value was defined as the IC_{50}. Examples of IC_{50} values determined by this method are specified in Table 6.

Inhibition of CETP Activity In Vivo.

Inhibition of CETP by a test compound can be determined by administering the compound to an animal by intravenous injection, determining the rate of transfer of tritium-labeled cholesteryl ester ([^{3}H]CE) from HDL to VLDL and LDL particles, and comparing the rate of transfer with the rate of transfer observed in control animals. Male golden Syrian hamsters were maintained on a diet of chow containing 0.24% cholesterol for at least

BNSDOCID: <WO 9914204A1 | >

two weeks prior to the study. Immediately before the experiment, animals were anesthetized with pentobarbital. Anesthesia was maintained throughout the experiment. Indwelling catheters were inserted into the jugular vein and carotid artery. Test compound was dissolved as a 80 mM stock solution in vehicle (2% ethanol: 98% PEG 400, Sigma Chemical Company, St. Louis, Missouri, USA). At the start of the experiment all animals received 0.2 ml of a solution containing [^{3}H]CE-HDL into the jugular vein. [^{3}H]CE-HDL is a preparation of human HDL containing tritium-labeled cholesteryl ester, and was prepared according to the method of Glenn et al. (Meth. Enzymol., 263, 339-351 (1996)). After 2 minutes, animals received 0.1 ml of the test solution injected into the jugular vein. Control animals received 0.1 ml of the vehicle solution without test compound. After 5 minutes, the first blood samples (0.5 ml) were taken from the carotid artery and collected in standard microtainer tubes containing ethylenediame tetraacetic acid. Saline (0.5 ml) was injected to flush the catheter and replace blood volume. Subsequent blood samples were taken at two hours and four hours by the same method. Blood samples were mixed well and kept on ice until the completion of the experiment. Plasma was obtained by centrifugation of the blood samples at 4° C. The plasma (50 µl) was treated with 5 µl of precipitating reagent (dextran sulfate, 10 g/l; 0.5 M magnesium chloride) to remove VLDL/LDL. After centrifugation, the resulting supernatant (25 µl) containing the HDL was analyzed for radioactivity using a liquid scintillation counter. The percentage [^{3}H]CE transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity

BNSDOCID: <WO__9914204A1_I_>

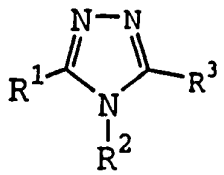
in equivalent serum samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 20 to 35% after 4 hours. The polyethylene glycol vehicle was determined to have no effect on CETP activity in this model.

Table 6 shows the results of experiments utilizing compounds of the present invention. Student t tests were performed to determine if the means for control and treated animals were statistically different. Values of $p < 0.01$ for both sets of data indicate that the differences are highly significant. The term "ND" means not determined.

BNSDOCID: <WO 9914204A1 I >

BNSDOCID: <WO___9914204A1_I_>

TABLE 6



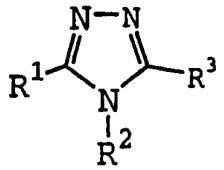
Example No.	R^1	R^2	R^3	CETP IC_{50} (μM)	Human Serum IC_{50} (μM)
1	*n*-$C_{13}H_{27}$-	3-CH_3O-C_6H_4-	-SH	2	50
2	*n*-$C_{13}H_{27}$-	2-F-C_6H_4-	-SH	3	125
3	*n*-$C_{13}H_{27}$-	2-CH_3-C_6H_4-	-SH	4	45
4	*n*-$C_{13}H_{27}$-	3-Cl-C_6H_4-	-SH	5	62
5	*n*-$C_{13}H_{27}$-	2-CH_3O-C_6H_4-	-SH	7	70
6	*n*-$C_{13}H_{27}$-	3-CH_3-C_6H_4-	-SH	7	150
7	*n*-$C_{13}H_{27}$-	cyclohexyl-	-SH	7	>500
8	*n*-$C_{13}H_{27}$-	4-F-C_6H_4-	-SH	8	200
9	*n*-$C_{13}H_{27}$-	4-C_6H_5O-C_6H_4-	-SH	8	500
10	*n*-$C_6H_{13}CC(CH_2)_5$-	3-CH_3O-C_6H_4-	-SH	8	>200
11	*n*-$C_{13}H_{27}$-	3-F-C_6H_4-	-SH	9	90

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO 9914204A1 I >

036

TABLE 6 (cont.)



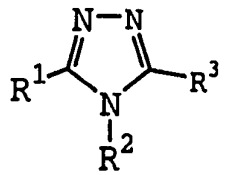
Example No.	R^1	R^2	R^3	CETP IC_{50} (μM)	Human Serum IC_{50} (μM)
12	*n*-$C_{13}H_{27}$-	3,4-(OCH_2O)-C_6H_3-	-SH	10	150
13	*n*-$C_{13}H_{27}$-	4-CH_3-C_6H_4-	-SH	10	175
14	*n*-$C_{13}H_{27}$-	2-Cl-C_6H_4-	-SH	10	250
15	*n*-$C_{13}H_{27}$-	4-CH_3O-C_6H_4-	-SH	10	290
16	*n*-$C_{13}H_{27}$-	3-CF_3-C_6H_4-	-SH	10	500
17	*n*-$C_{13}H_{27}$-	4-Cl-2-CH_3-C_6H_3-	-SH	10	>500
18	*n*-$C_{13}H_{27}$-	2-CH_3S-C_6H_4-	-SH	10	>200
19	*n*-$C_{13}H_{27}$-	4-$C_6H_5CH_2O$-C_6H_4-	-SH	15	>500
20	*n*-$C_{13}H_{27}$-	2-naphthyl-	-SH	15	ND
21	*n*-$C_{13}H_{27}$-	4-Cl-C_6H_4-	-SH	15	ND
22	$CH_3(CH_2)_6S(CH_2)_5$-	3-CH_3O-C_6H_4-	-SH	15	ND

SUBSTITUTE SHEET (RULE 26)

BNSDOCID: <WO___9914204A1_I_>

SUBSTITUTE SHEET (RULE 26)

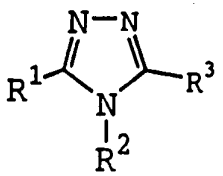
ACTIVITY TABLE 6 (cont.)



Example No.	R^1	R^2	R^3	CETP IC_{50} (μM)	Human Serum IC_{50} (μM)
23	$HCC(CH_2)_{11}$-	3-CH_3O-C_6H_4-	-SH	15	ND
24	*n*-$C_{13}H_{27}$-	3-CH_3-C_6H_4- •HNO_3	-H	20	>500
25	*n*-$C_{13}H_{27}$-	4-CH_3-3-Cl-C_6H_3-	-SH	20	>500
26	*n*-$C_{13}H_{27}$-	4-CH_3O-C_6H_4- •HNO_3	-H	20	ND
27	*n*-$C_{13}H_{27}$-	2-CH_3O-C_6H_4- •HNO_3	-H	20	ND
28	*n*-$C_{13}H_{27}$-	4-CF_3-C_6H_4-	-SH	20	ND
29	$CH_3(CH_2)_{10}OCH_2$-	3-CH_3O-C_6H_4-	-SH	20	ND
30	*n*-$C_{14}H_{29}$-	3-CH_3O-C_6H_4-	-SH	25	ND
31	*n*-$C_{12}H_{25}$-	3-CH_3O-C_6H_4-	-SH	25	ND
32	*n*-$C_{13}H_{27}$-	C_6H_5-	-SH	30	>500
33	*n*-$C_{13}H_{27}$-	2-naphthyl- •HNO_3	-H	30	ND

SUBSTITUTE SHEET (RULE 26)

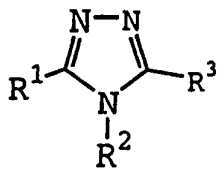
TABLE 6 (cont.)



Example No.	R^1	R^2	R^3	CETP IC_{50} (μM)	Human Serum IC_{50} (μM)
34	4-(n-C_8H_{17})$C_6H_4CH_2$-	3-CH_3O-C_6H_4-	-SH	35	ND
35	n-$C_{11}H_{23}$-	3-CH_3O-C_6H_4-	-SH	35	ND
36	n-$C_{13}H_{27}$-	3-$C_6H_5CH_2OC_6H_4$-	-SH	40	ND
37	$CH_3CH_2S(CH_2)_{10}$-	3-CH_3O-C_6H_4-	-SH	40	ND
38	$CH_3(CH_2)_{10}SCH_2$-	3-CH_3O-C_6H_4-	-SH	40	ND
39	n-$C_{13}H_{27}$-	3,4-(OCH_2O)-C_6H_3- •HNO_3	-H	45	ND
40	n-$C_{13}H_{27}$-	3,5-$(CH_3O)_2$-C_6H_3-	-SH	50	ND
41	n-$C_{13}H_{27}$-	3-pyridyl-	-SH	50	ND
42	n-$C_{13}H_{27}$-	2-CH_3CH_2O-C_6H_4-	-SH	50	ND
43	n-$C_{13}H_{27}$-	2,6-$(CH_3)_2$-C_6H_3-	-SH	50	ND
44	n-$C_{15}H_{31}$-	3-CH_3O-C_6H_4-	-SH	50	ND

BNSDOCID: <WO___9914204A1_I_>

TABLE 6 (cont.)



Example No.	R^1	R^2	R^3	CETP IC_{50} (μM)	Human Serum IC_{50} (μM)
783	4-(*n*-$C_{10}H_{21}$benzyl)-	3-CH_3O-C_6H_4-	-SH	4.5	ND
784	4-(*n*-C_9H_{19}benzyl)-	3-CH_3O-C_6H_4-	-SH	6	ND
785	4-(*n*-C_7H_{15}benzyl)-	3-CH_3O-C_6H_4-	-SH	6	ND
789	4-(n-C_8H_{17})$C_6H_4OCH_2$-	3-CH_3O-C_6H_4-	-SH	15	ND
790	4-(n-C_7H_{15})$C_6H_4OCH_2$--	3-CH_3O-C_6H_4-	-SH	20	ND
791	4-(n-C_6H_{13})$C_6H_4OCH_2$-	3-CH_3O-C_6H_4-	-SH	25	ND
794	4-(n-C_8H_{17})$C_6H_4(CH_2)_3$-	3-CH_3O-C_6H_4-	-SH	4	ND
795	4-(n-C_7H_{15})$C_6H_4(CH_2)_3$-	3-CH_3O-C_6H_4-	-SH	7.5	ND
796	4-(n-C_6H_{13})$C_6H_4(CH_2)_3$-	3-CH_3O-C_6H_4-	-SH	20	ND

SUBSTITUTE SHEET (RULE 26)

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent. The compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in co-therapy with one or more cardiovascular agents, such as compounds that lower serum cholesterol concentrations including inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors such as the statins (atorvastatin, cerivastatin, pravastatin, simvastatin, fluvastatin and lovastatin), inhibitors of squalene synthase, oxido squalene cyclase or inhibitors of other enzymes involved with cholesterol biosynthesis; inhibitors of the ileal bile acid transport protein (IBAT), cholesterol

BNSDOCID: <WO 9914204A1 >

absorption antagonists, ACAT inhibitors, bile acid sequestrants such as Cholestyramine and Cholestagel, fibrates such as Gemfibrozil, niacins such as Niaspan, and omega-3 fatty acids such as Omacor. Compounds of the present invention can also be used in co-therapy with cardiovascular drugs that reduce hypertension such as Enalopril and Captopril, or with anti-diabetes drugs such as troglitazone, or with antithrombotic agents such as aspirin, warfarin, and glycoprotein IIbIIIa antagonists such as Reopro, Xemilofiban and Orbofiban. The compounds of this invention can also be used in co-therapy with agents which lower serum triglyceride concentrations, including inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors such as the statins (atorvastatin), fibrates such as Gemfibrozil, niacins such as Niaspan, and omega-3 fatty acids such as Omacor.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent which will achieve the goal of improvement in disease severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions

BNSDOCID: <WO___9914204A1_I_>

of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously

BNSDOCID: <WO 9914204A1 >

from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut

INSDOCID: <WO___9914204A1_I_>

fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents ~~mentioned for use in the formulations~~ for oral

BNSDOCID: <WO__9914204A1_I_>

administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

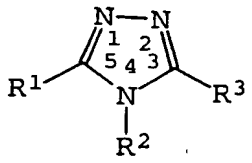
All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

BNSDOCID: <WO 9914204A1 | >

What is claimed is:

1. A compound of Formula I:



I

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl or 4-methylphenyl when R^1 is higher alkyl and when R^3 is -SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

2. A compound of Claim 1 wherein R^1 is selected from C_{10-15} alkyl, C_{10-15} alkenyl, C_{10-15} alkynyl, aryl, aryl-C_{1-12}-alkyl, aryloxy-C_1-C_{12}-alkyl, arylthio-C_1-C_{12}-alkyl, higher alkoxyalkyl, higher alkylthioalkyl, and cycloalkyl-C_{1-12}-alkyl; wherein R^2 is selected from aryl, 5-6 membered heteroaryl, lower cycloalkyl and lower cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower alkoxy,

BNSDOCID: <WO___9914204A1_I_>

halo, lower haloalkyl, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, aryloxy, lower aralkoxy, aryl, lower aralkyl, aminosulfonyl, amino, lower monoalkylamino and lower dialkylamino; and wherein R^3 is selected from -SH, chloro and hydrido; or a pharmaceutically-acceptable salt or tautomer thereof.

3. A compound of Claim 2 wherein R^1 is selected from tridecyl, undecyl, dodecyl, tetradecyl, pentadecyl, (heptylthio)pentyl, methoxyundecyl, dodecynyl, tridecynyl, tetradecynyl, (heptylphenyl)methyl, (octylphenyl)methyl, (nonylphenyl)methyl, (decylphenyl)methyl, (hexylphenoxy)methyl, (octylphenoxy)methyl, heptylphenyoxy)methyl, (hexylphenyl)propyl, (octylphenyl)propyl, (heptylphenyl)propyl, decylthiomethyl, undecylthiomethyl, ethylthiodecyl, and (undecyloxy)methyl; wherein R^2 is selected from cyclohexyl, naphthyl, pyridyl, and phenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from lower alkyl, lower alkoxy, halo, lower haloalkyl, phenoxy, methylenedioxy, benzyloxy, lower alkylthio, and lower dialkylamino; and wherein R^3 is SH; or a pharmaceutically acceptable salt or tautomer thereof.

4. A compound of Claim 3 wherein R^1 is selected from undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, tridecynyl, (heptylphenyl)methyl, (octylphenyl)methyl, (nonylphenyl)methyl, (decylphenyl)methyl, (heptylphenyl)propyl and (octylphenyl)propyl; wherein R^2 is selected from cyclohexyl, naphthyl, and phenyl, wherein R^2 is substituted by one or more radicals independently selected from methyl, fluoro, chloro, methylthio, benzyloxy, phenoxy,

BNSDOCID: <WO___9914204A1_I_>

methoxy, ethoxy, methylenedioxy, and trifluoromethyl; and wherein R^3 is SH; or a pharmaceutically acceptable salt or tautomer thereof.

5. A compound of Claim 1 selected from compounds and their pharmaceutically acceptable salts and tautomer of the group consisting of:

2,4-dihydro-4-(3-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-fluorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-cyclohexyl-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-pyridyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-ethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2,6-dimethylphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-phenoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(1,3-benzodioxol-5-yl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(2-chlorophenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-methoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

BNSDOCID: <WO___9914204A1_I_>

2,4-dihydro-5-tridecyl-4-(3-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(3-fluorophenyl)-3H-1,2,4-triazole-3-thione;

4-(3-chloro-4-methylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(4-benzyloxyphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-tridecyl-4-(4-trifluoromethylphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(1-naphthyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(4-methylthiophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3,4-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2,5-dimethoxyphenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(2-methoxy-5-chlorophenyl)-5-tridecyl-3H-1,2,4-triazole-3-thione;

4-(4-aminosulfonylphenyl)-2,4-dihydro-5-tridecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-dodecyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-tetradecyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-undecyl-3H-1,2,4-triazole-3-thione; and

2,4-dihydro-(4-methoxyphenyl)-5-pentadecyl-3H-1,2,4-triazole-3-thione.

BNSDOCID: <WO___9914204A1_I_>

6. A compound of Claim 3 wherein R^1 is selected from (heptylthio)pentyl, tridecynyl, (undecyloxy)methyl, ethylthiodecyl, (heptylphenyl)methyl, (octylphenyl)methyl, (nonylphenyl)methyl, (decylphenyl)methyl, (heptylphenyl)propyl, (octylphenyl)propyl, and undecylthiomethyl; wherein R^2 is methoxyphenyl; and wherein R^3 is -SH; or a pharmaceutically acceptable salt or tautomer thereof.

7. A compound of Claim 6 selected from compounds and pharmaceutically acceptable salts thereof of the group consisting of:

2,4-dihydro-5-(heptylthio)pentyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(tridecyn-12-yl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(tridec-6-ynyl]-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(undecyloxy)methyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(ethylthio)decyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-4-(3-methoxyphenyl)-5-(4-octylphenyl)methyl-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-heptylphenyl)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-nonylphenyl)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

5-(4-decylphenyl)methyl-2,4-dihydro-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-hexylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-heptylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-octylphenoxy)methyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;

2,4-dihydro-5-(4-hexylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione;
2,4-dihydro-5-(4-heptylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione; and
2,4-dihydro-5-(4-octylphenyl)propyl-4-(3-methoxyphenyl)-3H-1,2,4-triazole-3-thione.

8. A compound of Claim 3 wherein R^1 is tridecyl; wherein R^2 is selected from naphthyl, methylphenyl, methoxyphenyl, and benzodioxolyl; and wherein R^3 is hydrido; or a pharmaceutically acceptable salt or tautomer thereof.

9. A compound of Claim 8 selected from compounds, and tautomers of the group consisting of:
4-(2-naphthyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;
4-(3-methylphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;
4-(3-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;
4-(4-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate;
4-(2-methoxyphenyl)-3-tridecyl-4H-1,2,4-triazole, nitrate; and
4-(1,3-benzodioxol-5-yl)-3-tridecyl-4H-1,2,4-triazole, nitrate.

10. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 1.

11. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 2.

12. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 3.

13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 4.

14. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 5.

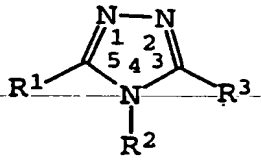
15. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 6.

16. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 7.

17. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 8.

18. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compounds selected from a family of compounds of Claim 9.

19. A method for treatment and prophylaxis of coronary artery disease comprising administering to the subject a therapeutically-effective amount of a compound of Formula I'



I'

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl,

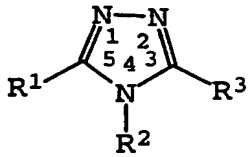
alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl when R^1 is tridecyl and when R^3 is SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

20 A method for increasing plasma levels of low density lipoproteins and decreasing plasma levels of high density lipoproteins by administering to the subject a therapeutically effective amount of a compound of Formula I'



I'

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

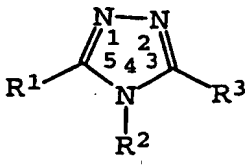
wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl when R^1 is tridecyl and when R^3 is SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

21. A method for inhibiting the activity of cholesteryl ester transfer protein in vivo by administering to the subject a therapeutically effective amount of a compound of Formula I'



I'

wherein R^1 is selected from higher alkyl, higher alkenyl, higher alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, and cycloalkylalkyl;

wherein R^2 is selected from aryl, heteroaryl, cycloalkyl, and cycloalkenyl, wherein R^2 is optionally substituted at a substitutable position with one or more radicals independently selected from alkyl, haloalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy, halo, aryloxy, aralkyloxy, aryl, aralkyl, aminosulfonyl, amino, monoalkylamino and dialkylamino; and

wherein R^3 is selected from hydrido, -SH and halo;

provided R^2 cannot be phenyl when R^1 is tridecyl and when R^3 is SH;

or a pharmaceutically-acceptable salt or tautomer thereof.

INTERNATIONAL SEARCH REPORT

Inter .al Application No
PCT/US 98/18170

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D249/12 C07D249/10 C07D249/08 C07D401/04 C07D405/04
A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BISGAIER C L ET AL: "Cholesteryl ester transfer protein inhibition by PD 140195" LIPIDS, vol. 29, no. 12, 1 December 1994, pages 811-818, XP000568834 cited in the application see the whole document	1-21
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002084533 see BRN 3038921, 3003084, 3002918, 3002594, 3002515 and 3000448 & J. PRAKT. CHEM., vol. 311, 1969, page 523	1,2

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 1998	21/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

4

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 98/18170

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 123, no. 19, 6 November 1995 Columbus, Ohio, US; abstract no. 256603m, KUDAN S M ET AL: "Synthesis of 2-alkyl-5-mercaptotriazoles and their derivatives as antibacterial and antifungal agents" page 1145; XP002084530 see abstract -& CHEMICAL ABSTRACTS, 13TH COLLECTIVE CHEMICAL SUBSTANCE INDEX, XP002084536 see page 948, middle column, 2nd compound; page 967, middle column, 21st compound; page 952, middle column, 7th compound & ORIENT. J. CHEM., vol. 11, no. 1, 1995, pages 59-62,	1,2,10, 11
X	CHEMICAL ABSTRACTS, vol. 114, no. 5, 4 February 1991 Columbus, Ohio, US; abstract no. 42664x, DAULATABAD C D : "Oleochemicals. II: synthesis and biological evaluation of some substituted 1,3,4-oxadiazoles and 1,2,4,4H-triazoles" page 732; XP002084531 cited in the application see abstract & J. OIL TECHNOL. ASSOC. INDIA (BOMBAY), vol. 21, no. 1, 1989, pages 27-9,	1,2,10, 11
X	CHEMICAL ABSTRACTS, vol. 95, no. 5, 3 August 1981 Columbus, Ohio, US; abstract no. 42999z, SANTUS M: "Synthesis of five-membered heterocycles. Reaction of 2-pyridyl isothiocyanate with amidrazone hydrochlorides" page 751; XP002084532 see abstract & ACTA POL. PHARM., vol. 37, no. 3, 1980, pages 293-300,	1,2,10, 11
X	FR 2 546 887 A (UNIVERSITE PARIS 7) 7 December 1984 see the whole document	1,2
X	GB 1 287 899 A (ROHM AND HAAS COMPANY) 6 September 1972 see the whole document	1,2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...l Application No
PCT/US 98/18170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2546887 A	07-12-1984	NONE	
GB 1287899 A	06-09-1972	BE 738433 A	04-03-1970
		CA 934381 A	25-09-1973
		CA 943554 A	12-03-1974
		CH 517106 A	31-12-1971
		CS 191860 B	31-07-1979
		DE 1966473 A	09-11-1972
		DE 1966806 A	12-06-1974
		DE 1967181 B	28-06-1979
		DE 1943915 A	12-03-1970
		FR 2019405 A	03-07-1970
		GB 1288540 A	13-09-1972
		JP 48029135 B	07-09-1973
		NL 6913528 A	06-03-1970
		US 4271308 A	02-06-1981
		US 3701784 A	31-10-1972
		US 3769411 A	30-10-1973
		US 3795679 A	05-03-1974
		AT 307148 B	15-03-1973
		BG 18170 A	02-09-1974

INTERNATIONAL SEARCH REPORT

Int...ational application No.
PCT/US 98/18170

Box I Observations where certain claims were found unsearchable (Continuation of item 1 f first she t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No prot st accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

Although all claims have been searched, the following should be noted:

The search revealed such a large number of particularly relevant documents, especially with regard to novelty of claims 1, 2, 10 and 11, that the drafting of a comprehensive international search report is not feasible. The cited documents are considered as to form a representative sample of the revealed documents, duly taking into account their relevance with respect to the subject-matter as illustrated by the examples.

BNSDOCID: <WO___9914204A1_I_>

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

Although all claims have been searched, the following should be noted:

The search revealed such a large number of particularly relevant documents, especially with regard to novelty of claims 1, 2, 10 and 11, that the drafting of a comprehensive international search repart is not feasible. The cited documents are considered as to form a representative sample of the revealed documents, duly taking into account their relevance with respect to the subject-matter as illustrated by the examples.